Journal of Integral Sciences [JIS]
[An International Open Access Journal]
Available at www.jisciences.com ISSN: 2581-5679

Formulation development and evaluation of bilayered tablets of amlodipine as immediate release layer and metaclopromide as sustained release layer

K.Vinod Kumar[1], B.Thangabalan[2], Dudekula Saidu Hussaian[3]
[1]Professor, SIMS College of Pharmacy, Guntur
[2]Principal, SIMS College of Pharmacy, Guntur
[3]SIMS College of Pharmacy, Guntur

Received: 11 Sept 2024 Revised: 28 Sept 2024 Accepted: 15 Dec 2024

Abstract
In the present study an attempt was made to prepare bilayer tablets of Amlodipine Besylate and Metoclopromide Succinate sustained release layer, which remains in stomach for prolonged period of time in a view to maximize bioavailability of drug, by using various concentrations of polymers, fifteen formulations of Metoclopromide having polymers at different concentration levels were prepared of which three formulations F8, F10, F13 showed excellent drug release profiles so these formulations were selected for the preparation of bilayer floating tablets. Amlodipine Besylate layer (immediate release) A1 was prepared by using sodium starch glycolate as super disintegrant, which showed excellent drug release so the composition of immediate release layer is kept constant in all formulations. Best formulations from both the layers were selected and formulated as bilayer tablets i.e (A1+F8), (A1+F10), (A1+F13) and these formulationsshowed excellent post compression C invitro drug release, hence all the three formulations were selected asoptimized formulations.

Keywords: Benecel K200M, Amlodipine Besylate, Metoclopromide Succinate, HPMC K4M.

Corresponding Author
Dr. K.Vinod Kumar

DOI: https://doi.org/10.37022/jis.v7i4.95

Produced and Published by
South Asian Academic Publications

Introduction

An Oral Dosage Form is the physical form of a dose of a chemical compound used as a drug or medication intended for administration or consumption by oral route. Common oral dosage forms are tablets or capsules. Tablets are solid preparations each containing a single dose of one or more active substances with or without excipients usually obtained by compressing uniform volumes of particles. Tablets are intended for oral administration. Some are swallowed whole, some after being chewed, some are dissolved or dispersed in water before being administered and some are retained in the mouth where the active substance is liberated. The excipients can include binders, glidants and lubricants to ensure efficient tabletting; disintegrates to promote tablet break-up in the digestive tract; sweeteners or flavors to enhance taste; and pigments to make the tablets visually attractive. These are included in the formulations to facilitate easy handling, enhance the physical appearance, and improve stability and aid in the delivery of the drug to the blood stream after administration. A polymer coating is often applied to make the tablet smoother and easier to swallow, to control the release rate of the active ingredient, to make it more resistant to the environment (extending its shelf life), or to enhance the tablet's appearance.

Immediate Release Tablets

The need for new oral drug delivery system continues, due to poor patient acceptance for invasive methods, need for exploration of new market for drugs and coupled with high cost of disease management. Developing new drug delivery techniques and utilizing them in product development is critical for pharma companies to survive this century.

An immediate release dosage form allows a manufacturer to extend market exclusivity, while offering patients a convenient dosage form or dosage regimen.Immediate Release Tablets are those tablets which are designed to disintegrate and release their medication with no special rate controlling features, such as special coatings and other techniques.

Recently immediate release tablets have started gaining popularity and acceptance as a drug delivery system, mainly because they are easy to administer, has quick onset of action is economical and lead to better patient compliance. They are also a tool for expanding markets, extending product life cycles and generating opportunities.

Advantages of Immediate Release Tablets –

- Economical and cost effective.
- Quick onset of action.

- Suitable for industrial production.
- Improved stability and bioavailability. Disadvantages of Immediate Release Tablets –
- Rapid drug therapy intervention is not possible.
- Sometimes may require more frequency of administration.
- Dose dumping may occur.
- Reduced potential for accurate dose adjustment.

Introduction to sustained release formulation

For decades an acute or chronic illness is being clinically treated through delivery of drugs to the patients in form of some pharmaceutical dosage forms like tablets, capsules, liquids, creams, pills, aerosols, injectables, and suppositories. However, these conventional dosage forms have some drawbacks. Multiple daily dosing is inconvenient to the patient and can result in missed doses, made up doses and patient incompliance with the therapeutic regimen. When conventional immediate release dosage forms are taken on schedule and more than once daily, there are sequential therapeutically blood peaks and valley associated with taking each dose. It should be emphasized.

Advantages of sustained release formulations

- Reduction in dosing frequency.
- Reduced fluctuation in circulatory drug levels.
- Avoidances of night time dosing.
- Increased patient compliance.
- More uniform effect.

Disadvantages of sustained release formulations:

- High cost.
- Dose dumping.
- Reduced potential for dosage adjustments.
- Increased first pass clearance.

Bilatered Tablets

Bilayered 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. Bilayered 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 bi-layer tablets, 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.

For the supervision of fixed dose combinations of drugs, prolong the drug product life cycle, buccal /mucoadhesive delivery systems, manufacture novel drug delivery systems such as chewing device and floating tablets for gastro-retentive drug delivery systems.

- Controlling the delivery rate of either single or two different API'S.
- To adapt the total surface area available for API layer either by sandwiching withone or two inactive layers in order to achieve swell able / erodible barriers for controlled release.
- To separate incompatible API's with each other, to control the release of onelayer
  by utilizing the functional property of the other layer .

Advantages of Bilayer tablets

- Release of both drugs starts immediately.
- Combination of incompatible drugs. Physical-chemical incompatibility can be prevented by physical separation of two drugs.
- Combination of different release profiles. Immediate release and sustained release profile can be achieved in single tablet by forming immediate release layer and sustained release layer.
  Prospective use of single entity feed granules.
- Greatest chemical and microbial stability over all oral dosage form.
- Objectionable odour and bitter taste can be masked by coating technique.
- Belayed execution with optional single - layer conversion kit.
- Low cost compared to all other dosage form.
- Offer greatest precision and least content uniformity.

General Properties of Bilayer Tablet

Dosage Form

- It should have sufficient strength to withstand mechanical shock during its production, packaging, shipping and dispensing.
- It should have graceful product identity free of defects like chips, cracks, discoloration and contamination.
- Must have a chemical stability shelf life, so as not to fallow alteration of the medicinal agents.
- The bilayer tablet must release drug in a expectable and reproducible manner.

Various Techniques for Preparation of Bilayertablets: En So TROL Technology

Solubility enhancement of an order of magnitude or to create optimized dosage form Shire laboratory use an integrated approach to drug delivery focusing on identification and incorporation of the identified enhancer into controlled release technologies.28,29

EN SO TROL Technologies

OROS® Push Pull Technology

This system consist of mainly two or three layer among which the one or more layer are essential of the drug and other layer are consist of push layer. Thedrug layer mainly consists of drug along with two or more different agents. So this drug layer comprises of drug which is in poorly soluble form. There is further addition of suspending agent and osmotic agent. A semi permeable membrane surrounds the tablet core. 28

L-OROS tm technology

This system used for the solubility issue Alza developed the L-OROS system where a lipid soft gel Product containing drug in a dissolved state is initially manufactured and then coated with a barrier membrane, than osmotic push layer and than a semi permeable membrane, drilled with an exit orifice.

Duros Technology

The system consists from an outer cylindrical titanium alloy reservoir. This reservoir has high impact strength and protects the drug molecules from enzymes. The DUROS technology is the miniature drug dispensing system that opposes like a miniature syringe and reglious minute quantity of concentrated form in continuesand consistent from over months or Year. 28, 30

DUROS Technology Types of bi-layer tablet presses

- Single sided tablet press.

- Double sided tablet press.
- Bi-layer tablet press with displacement.
- Single sided tablet press:

Bilayer tablet press with displacement

The displacement tablet weight control principle is fundamentally different from the principle based upon compression force. When measuring displacement the control system sensitivity does not depend on the operation point. But depends on the applied pre-compression force. In fact the lower the pre-compression force, the more the monitoring control system and this ideal for good interlayer bonding of the bi-layer tablet. The upper pre-compression roller is attached to an air-piston which can move up and down in air cylinder. The air pressure in the cylinder is set as a product parameter at initial product set-up and is kept at a constant value by the machine's control system. This pressure multiplied by the piston surface is the constant force at which the piston and consequently the roller is pushed downwards against affixed stop. The lower pre- compression roller is mounted on a yoke and its vertical position can be adjusted through the control system by means of a servomotor. The position of the lower pre-compression determines the pre- compression height.

Advantages

- Weight monitoring/control for accurate and independent weight control ofthe individual layers.
- Low compression force exerted on the first layer to avoid capping andseparation of the two individual layers.
- Provide sufficient hardness at maximum turret speed.

Methodology

Formulation of Immidiate Release Amlodipine besylate Formulation Design

Amlodipine besylate tablets were prepared using direct compression technique. Different formulations of Amlodipine besylate were designed to be prepared by direct compression method using two super disintegrates (pregelatinized starch, crospovidone) keeping all other ingredients constant.

Procedure: Amlodipine besylate 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 final mixture was shaken manually for 5-10 min in a plastic bag. This powder was passed through the hopper of 16 station rotary tableting

Formulation code (mg)	FI 1	FI 2	FI 3	FI 4
Amlodipine besylate	10	10	10	10
Crospovidone	-	-	8	10
Pregelatinized starch	8	10	-	-
Lactose	68.5	66.5	68.5	66.5
Magnesium stearate	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5
Colouring agent (Fe_2o)	0 .50	0.50	0.50	0.50
Total weight (100 mg)	90	90	90	90

machine and punched into tablets using 8mm s/c. the process is similar for all core formulations, which are prepared by direct compression technique.

Formulation Code	Metaprolol succinate (mg)	Sodium CMC (mg)	Sodium Alginate (mg)	HPMC K4M (mg)	MCC (mg)	Magnesium Stearate (mg)	Talc (mg)	Total Weight (mg)
FS 1	10	15	_	_	124	3	3	160
FS 2	10	_	15	_	124	3	3	160
FS 3	10	_	_	15	124	3	3	160
FS 4	10	30	_	_	113	3	3	160
FS 5	10	_	30	_	113	3	3	160
FS 6	10	_	_	30	113	3	3	160
FS 7	10	45	_	_	98	3	3	160
FS 8	10	_	45	_	98	3	3	160
FS 9	10	_	_	45	98	3	3	160
FS 10	10	_	22.5	22.5	98	3	3	160
FS 11	10	22.5	_	22.5	98	3	3	160
FS 12	10	22.5	22.5	_	98	3	3	160

Formulation of Metaclopromide

Procedure: Metaclopromide and all other ingredients listed in Table except magnesium stearate, Finally, magnesium stearate, Talc was introduced to the powder mixture. The final mixture was shaken manually for 5-10 min in a plastic bag. This powder was passed through the hopper of 16 station rotary tableting machine and punched into tablets using 8mm s/c. the process is similar for all core formulations, which are prepared by direct compression technique.

Standard Calibration Curve:

Preparation of 1.2 PH Buffer: Take 2 gm of sodium chloride (Nacl), and 7 mL of hydro chloricacid (Hcl). And make upto 1000 mL with distilled water. It is used as 1.2 pH buffer. Preparation of standard graph: A standard graph of pure drug in suitable medium was prepared by plotting the concentrations on x- axis and absorbance values on y-axis. Procedure for standard graph of Amlodipine besylate: Accurately weighed amount of 100 mg of Amlodipine besylate is taken in a 100 mL volumetric flask. The volume was made up to 100 mL with distilled water, which constitutes the primary stock solution of 1 mg/mL. by further diluting this stock solution suitably with distilled water various concentrations like 1, 2, 3, 4, 5and 6 µg/mL were prepared. These solutions were checked for their absorbance using UV-visible spectrophotometer at λmax 237 nm against distilled water 1.2 pH buffer as blank and a standard graph was plotted.

Procedure for standard graph of Metaclopromide

Accurately weighed amount of 100 mg of Metaclopromide is taken in a 100 mL volumetric flask. The volume was made up to 100 mL with distilled water, which constitutes the primary stock solution of 1 mg/mL. by further diluting this stock solution suitably with distilled water various concentrations like 5,10,15,20 and25, µg/ml were prepared. These solutions were checked for their absorbance using UV visible spectrophotometer at λmax 254 nm against distilled water
6.8 pH buffer as blank and a standard graph was plotted

Evaluation of the tablets

Pre-compression parameters: Prior to the compression, the powder blends of various batches were evaluated for their bulk and tapped density and from these values compressibility index and Hausner ratio were calculated. While the flow properties of the powder bled were accessed from the angle of repose. The evaluation parameters were studied before and after addition of lubricants to check and compare the inherent flow

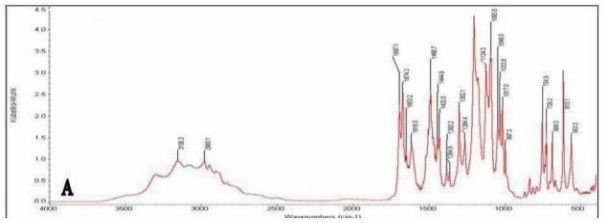
properties of powders.

Angle of repose ,Bulk density, Hardness , Friability

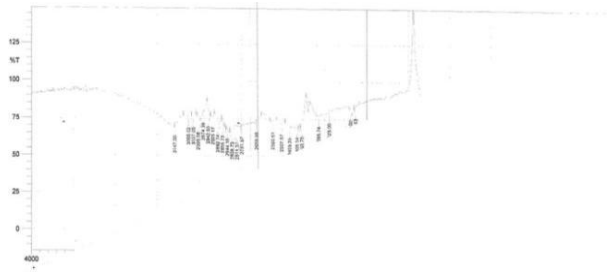
In vitro Release Studies: Dissolution Test: The dissolution test was conducted using intestine (pH-1.2) as dissolution medium for uncoated tablets (SaffarMansoor et al., 2007). Using simulated intestinal fluid 900 ml of 1.2 pH phosphate buffer was placed in the vessel and allowed to come to 37 ± 0.5 °C. Then, Amlodipine besylate tablets were placed in six baskets, one in each basket and stirrer was rotated at 75 rpm for 1 hr. After 5, 10, 15, 20, 25, 30, 40, 50 and 60 min, sample of 5 mL was pipette out and same volume of fresh 1.2 pH buffer was added to keep volume of the dissolution medium constant. Absorbance was measured at 237nm.

Results and Discussion

FTIR of Amlodepine Besylate



FTIR of Metoclopromide

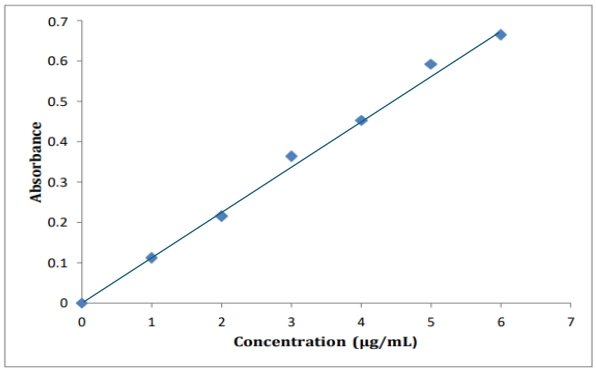


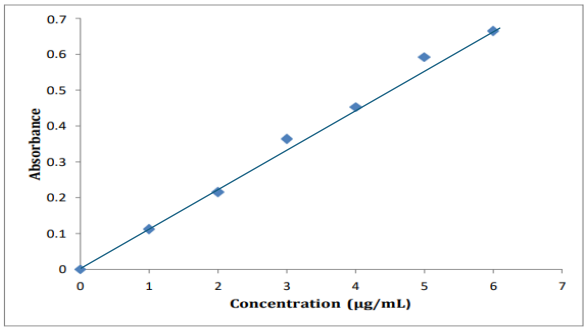
Standard Graph of Metoclopromide

Standard calibration curve of metoclopromide

Sr.No.	Concentration (ug/ml)	Absorbance
0	0	0
1	1	0.112
2	2	0.203
3	3	0.311
4	4	0.453
5	5	0.5G2

Table 5.3 Standard calibration curve of Amlodepine besylate





EVALUATION OF TABLETS:

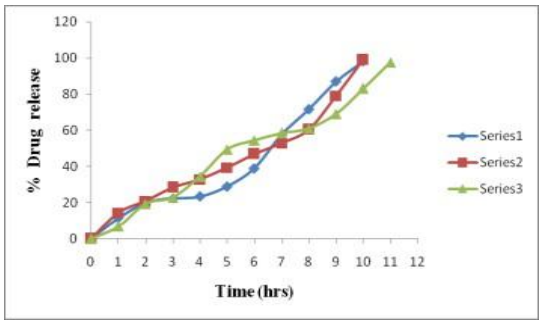
Pre-compression parameters for immediate release of Amlodepinebesylate :

Formulation code	Angle of Repose ( )	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	ausner's ratio	% Compressibility
F I 1	27.64	0.60	0.68	1.13	12.09
FI 2	29.00	0.59	0.68	1.14	13.74
FI 3	28.77	0.60	0.71	1.17	14.65
FI 4	26.11	0.63	0.70	1.12	11.46

Amlodepine besylate

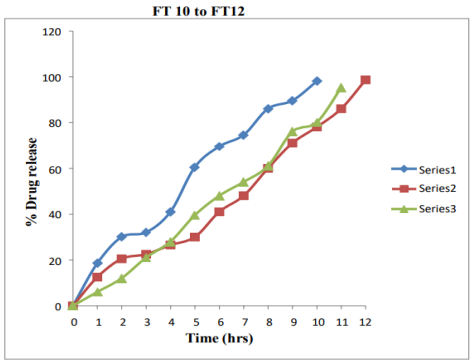
Pre-compression parameters of sustained release of metoclopromide

Formulation Code	Angle of epose( )	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	ausner's ratio	% Compressibility
FS1	25.46	0.61	0.74	1.21	16.71
FS2	27.76	0.59	0.6	1.13	13.69
FS3	23.3	0.63	0.72	1.14	14.60
FS4	30.86	0.60	0.68	1.12	13.91
FS5	26.00	0.62	0.70	1.13	14.25
FS6	24.03	0.63	0.70	1.12	12.81
FS7	24.33	0.60	0.71	1.17	14.11
FS 8	27.33	0.59	0.70	1.18	13.23
FS9	30.46	0.57	0.66	1.14	13.79
FS10	23.33	0.60	0.73	1.20	19.22
FS11	22.23	0.57	0.64	1.12	12.52
FS12	24.66	0.65	0.73	1.12	13.03



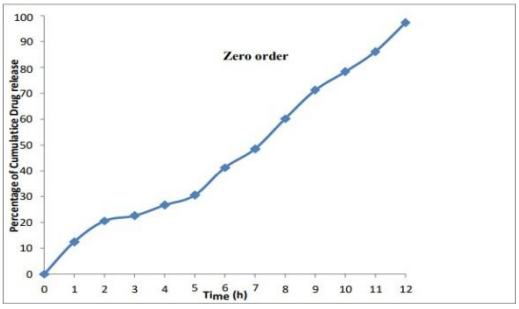
In vitro Dissolution profile of the formulations

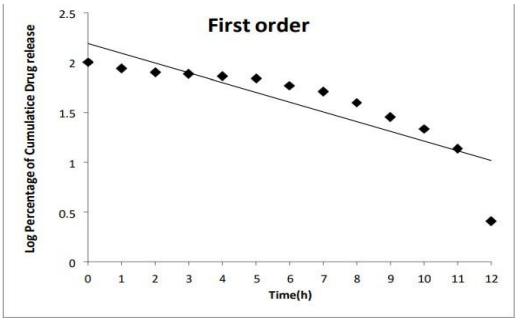
pH 6.8 Phosphate buffer, 900 mL ,USP-II (Basket) Apparatus,75 rpm, 37± 0.5 ^{0}C			
TIME (hrs)	% CDR	% CDR	% CDR
	FT 10	FT 11	FT 12
0	0	0	0
1	18.7	12.54	6.19
2	30.19	20.56	12.65
3	32.23	22.53	21.47
4	41.24	26.64	28.33
5	60.72	30.49	39.21
6	69.7	41.28	48.33
7	74.70	48.56	54.33
8	86.22	60.22	61.41
9	89.74	71.24	76.43
10	98.2	78.38	80.42
11		86.21	95.49
12		98.65	

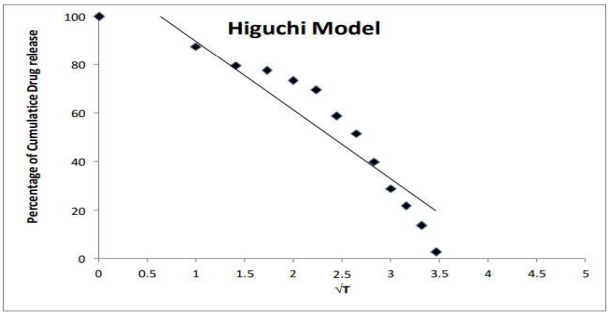


Optimised Formula

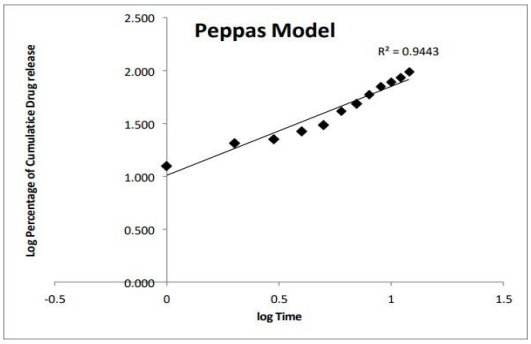
GRAPHS OF FT 11 FORMULATION:







Higuchi model of FT 11 formulation



Peppas model of FT 11 formulation

Released kinetics for all formulations:

Formulation code	Zero order	First order	Higuchi	Korse – mayer's	
	R^2	R^2	R^2	R^2	N
FT 1	0.9458	0.8365	0.9935	0.9945	0.585
FT 2	0.8592	0.9466	0.9842	0.9510	0.487
FT 3	0.9580	0.8030	0.9437	0.9065	0.560
FT 4	0.8492	0.7829	0.9616	0.9369	0.356
FT 5	0.9842	0.6971	0.9428	0.9873	0.765
FT 6	0.9768	0.9288	0.9518	0.9804	0.787
FT 7	0.9362	0.6567	0.7905	0.8964	0.919
FT 8	0.9540	0.5390	0.8530	0.9531	0.788
FT9	0.9815	0.7181	0.9135	0.9815	1.017
FT10	0.9809	0.8361	0.9461	0.9725	0.755
FT11	0.9807	0.7407	0.8740	0.9443	0.841
FT12	0.9932	0.7877	0.8859	0.9981	1.153

Stability studies

The formulation FT11 were selected for stability studies on the basis of their high cumulative % drug release and also results of in vitro disintegration time, wetting time, and in vitro dispersion studies. The stability studies were carried out at 40 0C / 75% RH for all the selected formulations up to 30 days. The tablets were analyzed for drug content uniformity, hardness, drug content and friability up to 30 days.

Selected Formulation for stability studies FT 11 stored at 40 ^{0}C / 75%RH.

Formulation code	Tested after time (in days)	Hardness (kg/cm2) *Mean SD (n=3)*	Drug content *Mean SD(n=3)*	Friability %
FT 11	10	4.66 ± 0.18	97.54 ± 0.11	0.4386
	20	4.66 ± 0.23	97.54 ± 0.17	0.4381
	30	4.66 ± 0.29	97.54 ± 0.22	0.4378

Discussion

Scanning of drug

The pure drug Amlodepine besylate was scanned over a range 200-400 nm to determineits λ max. The peak was observed at the 237 nm for Amlodepine besylate. The obtained results Conforms the identification of Amlodepine besylate in ethanol and distilled water.

Standard calibration curve of Amlodepine besylate:

dard calibration curve of Amlodepine besylate: The standard calibration curve of Amlodepine besylate was obtained byplotting Absorbance v/s. Concentration. The standard calibration curve shows the slope of 0.114 and correlation coefficient of 0.996.

Scanning of drug

The pure drug Metoclopromide was scanned over a range 200-400 nm to determine its λmax. The peak was observed at the 230 nm for Metoclopromide The obtained results Conforms the identification of Metoclopromide in ethanol and distilled water.

Standard calibration curve of Metoclopromide:

The standard calibration curve of Metoclopromide was obtained by plotting Absorbance v/s. Concentration. The standard calibration curve shows the slope of 0.011 and correlation coefficient of 0.999. The curve was found to be linear in the concentration range of 5, 10, 15, 20 and 25 µg/ml (Beer's range) at 230 nm.

Pre compression parameters

The Amlodepine besylate tablets were prepared direct compression method. The optimised formula is FI 4. Before compression the powder is evaluated for angle of repose, bulk density, tapped density, Hausner's ratio and compressibility index. The bulk density of the powder was found to be 00.63 gm/cm3 , while the tapped density was 0.70

±0.02 gm/cm3 .

Post compression

The bilayer tablets were prepared by direct compression method. The tablets were evaluated for their hardness, diameter, thickness, friability; disintegration and in vitro drug release . The Optimised formula was FT 11.

The stability studies were carried out at 40 0C / 75% RH for all the selected formulations up to 30 days. The tablets were analyzed for drug content uniformity, hardness, drug content and friability up to 30 days. These formulations showed not much variation in any parameter.

Conclusion

The present works involves formulation and development and optimizationand in-vitro evaluation of bilayer tablets of Amlodepine besylate and Metoclopramide. With fixed dose of Metoclopromide sustained release layer and Amlodepine besylate immediate release layer for treatment of hypertension. Under preformulation studies API (Active pharmaceutical ingredients) Characterization and drug excipients compatibility studies carried out. The results revel that the formulation FT 11 has met the objective of sustained release for over a period of 12 hours. The formulation FT 11 has met the desired in vivo C in vitro correlation limits as for USP

References

1. Banker GS, Anderson SN. Modern pharmaceutics. 4rd ed. New York: Taylor C Francis Group;2005.p.23-24.
2. Rudman A. Guidance for industry-Immediate release solid dosage forms. CDER1995 Nov; 59(83): 48754-59
3. Pandey VP, Manavalan R, Sundar RT and Ganaesh KS. Formulation and release characteristics of sustained release Diltiazem Hydrochloride tablet. Ind J Pharm Sci 2003; 65 (1): 44-48.
4. Chein YW, "Novel Drug Delivery Systems", 2nd edition, Marcel Dekker, NewYork:
   Madison Avenue, 1992, 139-96.
5. Herber.A.Lieberman, Leon Lachman, Joseph B.Schwetz, "Pharmaceutical dosage forms", vol: 1, 2nd edition, 179-181.
6. Sharma A, Jain A, Purohit A, Jatav R and Sheorey RV, "Formulation and evaluation of aceclofenac fast dissolving tablets", Int J Pharm C Life Sci, 2011,2 (4), 681-686.
7. Kulakarni A et al, Bhatia M. et al, Development and evaluation of bi-layerfloatingtablets of atenolol and lovastatin for biphasic release profile, Iran.J. Pharm. Res., 2009, 8: pp15- 25.
8. Nirmal J, Saisivam S, Peddanna C, Muralidharan S, Godwinkumar S andNagarajan M, 'Bilayer tablets of atorvastatin calcium and nicotinic acid:Formulation and evaluation", Chem Pharm Bull, 2008, 56, 1455-8.
   G. Maggi L, Segale L, Conti S, Ochoa Machiste E and Conte U, "Preparation and evaluation of release characteristics of TabGum: a novel chewing device", Eur JPharm Sci, 2005, 24, 487-93.
10. Notari, r., Biopharmaceutics and clinical pharmacokinetics,an introduction,3rd Ed.,Marcel Dekker inc.New York 1980,p.152-154
11. Panchal Hiten Ashok, Tiwari Ajay Kumar, A Novel Approach of Bi-layer Tablet Technology- a review, IRJP, 2012, Vol. 3(5), pp 44-49.

12. Rohan D. Deshpande, D. V. Gowda, Nawaz Mahammed and DeepakN. Maramwar, IJPSR, 2011, Vol.2(10), pp 2534-2544
13. Lechman L, Libermen H.A, Kanig J.L, "In The Theory and Practice of Pharmacy", 3rd Ed, Varghese Publishing House, Bombay, 1987, 430-453.
14. Divya .A, K. Kavitha, M. Rupesh Kumar, Dakshayani S, Jagadeesh Singh SD,"Bilayer tablet technology: An overview", Journal of Applied Pharmaceutical Science, 01 (08), 2011, 43-47.
15. Patel Mehul, Ganesh Nanjan Sockan, kavitha, Tamizh Mani, Challenges in the formulation of bi-layered tablets: a review, IJPRD, 2010, Vol. 2, pp 30-42.
16. Panchal Hiten Ashok, Tiwari Ajay Kumar, A Novel Approach of Bi-layer Tablet Technology- a review, IRJP, 2012, Vol. 3(5), pp 44-49.
17. Reddy Sunil, Panakanti Pavan kumar, Kandagatla Rajanarayana and Yamsani Madhusudan Rao. International J Pharmaceutical Sciences and Nanotechnology2010; 3: 1-4.
18. H.p rang ,m m dale ,jm ritter ,rj flower , Pharmacology , 6 th edition 2007 ,pg no 298- 310
1G. Tripathi KD. Essentials of medical pharmacology. 5th ed. New Delhi:Jaypee brothers medical publication (p) Ltd; 2003.
20. M. C. Gohel, R. K. Parikh, S. A. Nagori, 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
21. Akash Yadav, Dinesh Kumar Jain, Formulation development and in vitro characterization of bilayer and floating-bioadhesive tablets of propranolol hydrochloride,Asian Journal of Pharmacy C Life Science, 2011,Vol. 1 (1),pp 2-12.
22. M. Alagusundaram, C Madhusudhana Chetty, D. Dhachinamoorthi Development and evaluation of novel transbuccoadhesive bilayer tablets of Famotidine, 2011,Vol. 5(3), pp 150-156.
23. Girish S. Sonar, Devendra K. Jain, Dhananjay M. More, Preparation and invitro evaluation of bilayer and floatingbioadhesive tablets of rosiglitazone maleate, AsianJournal of Pharmaceutical Sciences, 2007, Vol. 2 (4), pp 161-169.
24. Kale V. V., Kasliwal R., Parida S. K., Awari J. G., Inter. J. Pharm.Exci., 32, 75—80 (2004) www.pubmet.com