Research Article **ISSN: 2349 – 4492**

Asian Journal of Research in Biological and Pharmaceutical Sciences

Journal home page: www.ajrbps.com

https://doi.org/10.36673/AJRBPS.2021.v09.i01.A05

FORMULATION DEVELOPMENT AND *IN-VITRO* EVALUATION OF BI-LAYERED IMMEDIATE RELEASE TABLETS OF PIOGLITAZONE AND GLIMEPIRIDE

Sunil Mekala[*1], Chitta Hari Krishna[1], Gandikota Naveen[1], Kelam Suresh Babu[1], Malla Bhavitha[1], N. Janapriya Lakshmi[1], Shaik Atiya Bhanu[1]

[1*]Department of Pharmaceutics, Vishwa Bharathi College of Pharmaceutical Sciences, Perecherla, Guntur, Andhra Pradesh, India.

ABSTRACT

The novel drug delivery systems where a combination of two or more drugs in a single unit having different release profiles which improves patient compliance and prolongs the drug action. Bilayered matrix tablets composed of two layers, one is immediate release and a second layer is extended release layers. The *In vitro* studies have shown more than 80% of pioglitazone was released within 60 min. Drug release mechanism exponent (n) was determined for all formulations (0.679-0.799). The release of pioglitazone were found to follow a first order release and glimepiride was found to be zero order release model.

KEYWORDS

Glimepiride, Pioglitazone, Sodium starch glycolate, Ethyl cellulose and HPMC K4M.

Author for Correspondence:

Sunil Mekala,

Department of Pharmaceutics,

Vishwa Bharathi College of Pharmaceutical Sciences,

Perecherla, Guntur, Andhra Pradesh, India.

Email: dr.sunilmekala@gmail.com

INTRODUCTON

The best new therapeutic entity in the world is of small value without an appropriate delivery system. Tablet delivery system can range from simple immediate release formulations to complex extended or modified release dosage forms. The important role of drug delivery system is the drug delivered to the site of action in sufficient amount and at the appropriate rate. However it should meet other important criteria such as physical and chemical stability, ability to be mass-produced in a manner that assures content uniformity.

Solid dosage forms

The Solid dosage forms are widely prevalent due to their age-old application. Especially, oral solid formulations hold a high potential as they serve to

be most convenient for the administration of drugs. The Pharmaceutical oral solid dosage forms have been used for decades mainly due to their convenience of administration and their suitability for delivery of drugs for systemic effects. The most commonly used in pharmaceutical solid dosage forms today include granules, pellets, tablets and capsules etc.

MATERIAL AND METHODS

Manufacturing process

Process for pioglitazone hydrochloride granulation

Dry mixing

Pioglitazone hydrochloride, lactose monohydrate, croscarmellose sodium loaded into RMG and mix for 10 min at slow mixer speed.

Preparation of binder

Hydroxy propyl cellulose was dissolved in purified water.

Wet granulation

Binder was added into RMG while mixing at slow mixer speed. Then mixer speed was changed to fast and continued till required consistency of mass is obtained.

Drying

Material was dried in FBD till required LOD was achieved.

Sifting

Dried granules were sifted through #40 mesh on single deck sifter. Coarse granules retained on #40 were milled through multimill using 1.5mm screen. Knives forward, fast speed and re-sifted through #40.

Blending

Before addition of lubricants

Granules were loaded into Octagonal blender (OGB) and blend it for 10 min.

After addition of lubricants

Lubricants were weighed and sifted through #40 and added into blender. Blend it for 5 min. A sample was analysed for physical parameters.

Process for glimepiride

Dry mixing

Glimepiride loaded into RMG along with lactose monohydrate, povidone and dry mix for 10 min.

Wet granulation

Purified water was added into RMG while mixing at slow mixer speed. Then mixer speed was changed to fast and continued till required consistency of mass is obtained.

Drying

Material was dried in FBD till required LOD was achieved.

Sifting

Dried granules were sited through #30mesh on single deck sifter. Coarse granules retained on #30 were milled through 2mm screen, Knivers forward.

Blending

Before addition of lubricants

Granules were loaded into Octagonal blender (OGB) and blend it for 10 min.

After addition of lubricants

Lubricants were weighed and sifted through #40 and added into blender. Blend it for 5min. A sample was analysed for physical parameters.

Compression of bi layer tablet

Two granules blends were placed in two different hoppers and compressed first layer followed by second layer to get bi layer tablets.

Compression punch description

Size: 8mm x 19.1mm.

Type: ROUND (convex)

Embossing: 254 at upper punch.

Score line: no score

Compression Force

Pre compression: 1.8-2.2 kN

Main compression: 16.9-21.4 k

COMPARATIVE DATA OF VARIOUS FORMULATIONS

Pioglitazone layer

Glimepiride layer

Experimental work

The following pre formulation studies were performed for the Methocarbamol and Acetaminophen bi layer tablet formulations.

Sieve Analysis

Pass a define mass of the sample through various sieves and calculate the percentage of retained powder and fines passed through sieves.

$$\text{Percentage of powder retained} = \frac{\text{Weight of the powder}}{\text{Total weight of the powder}} \times 100$$

Bulk density

It is the ratio between a given mass of powder and its bulk volume.

$$\text{Bulk density} = \frac{\text{Mass of powder}}{\text{Total weight of the powder}}$$

A given quantity of the powder is transferred to the measuring cylinder and it is tapped mechanically either manually or mechanical device till a constant volume is obtained. This volume is bulk volume (v) and it includes the true volume of the powder and void space among the powder particles.

Angle of repose

Angle of repose is define as the maximum angle possible between the surface of pile of powder and the horizontal plane. The granule mass should allowed to flow out of the funnel orifice on a plane paper kept on the horizontal surface. This forms a pile of granules on the paper.

$\tan \theta = h/r$

$\theta = \tan^{-1}(h/r)$

Where, h= height of the pile

r= radius of the pile

Tapped density

Tapped density is defined as the ratio between weight of the sample powder taken and the tapped volume.

Tapped density (ρt) = M/V_f

Where, M = weight of sample powder taken

V_f = tapped

Compressibility index

The bulk density and tapped density should measured and the compressibility index can calculated by using the following.

$C.I = \{(\rho_f - \rho_o)/\rho_t\} \times 100$

Where, ρ_f = tapped density

ρ_o = bulk density

Hausner ratio

By calculating tapped density and bulk density, the Hausner ratio can be calculated.

Hausner ratio = ρ_t / ρ_o

Where, ρ_t = tapped density

ρ_o = bulk density

RESULTS AND DISCUSSION

Pre-formulation study

Discussions

While measuring LOD, the temperature should fixed less than the melting point of the drugs.

Pioglitazone granules

- In F1 and F2 both compressibility index and Hausner ratio found poor.
- In F1 large granule came due to use of more amount of hydroxy propyl cellulose, so retained on pan is very less. From F3 hydroxy propyl cellulose used which having less viscosity and amount of binder also reduced.

Glimepiride granules

- In F2, F3, F4 both compressibility index and Hausner ratio found very poor due to poor granules formed during the granulation process.
- In F2, F3, F4 more fines came during granulation, so large amount of material passed through all sieves and retained in pan.
- In F2, F3, F4 more weight variation came due to rat-holing showed in glimepiride layer From F7 weight was decrease due to increase percentage of drug in the pioglitazone layer.

Bi layer tablets

- In F1 hardness was very high due to use of hydroxy propyl cellulose in high amount in pioglitazone layer and in glimepiride layer RMG process was used. In F6 hardness was slightly increased due to use of RMG process in glimepiride layer.
- In F1 DT was found very high due to less amount of Disintegrant used. Also a high amount of hydroxy propyl cellulose was used. In F6 DT increase due to large size granules came in glimepiride layer in RMG process.
- In F1 no friability was found due to over granulation and very hard granules came in pioglitazone layer during process. In F2, F3 and F4 friability was found high due to
- More fines came in glimepiride layer during process. Again in F6 friability found very less due to use of RMG in preparation of glimepiride granules.
- The study was undertaken with an aim to formulate combination of antidiabetic agents

as bilayer tablets. The literature shows that Pioglitazone is a potent and highly selective agonist for peroxisome proliferator-activated receptor-gamma (PPARγ). PPAR receptors are found in tissues important for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPARγ nuclear receptors modulates the transcription of a number of insulin-responsive genes involved in the control of glucose and lipid metabolism. It is mainly used in the treatment of type 2 diabetes.

Table No.1: List Tables of Comparative Data of Various Formulations

S.No	Trial	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
	Ingredient	**Composition mg/Tablet**									
1	Glimepiride	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
2	Lactose(pharmatose200m)	55.2	55.2	56.2	56.2	56.2	56.2	56.2	56.2	56.2	56.2
Binder											
3	Povidone k 30	5.5	5.0	4.5	4.0	3.5	3.0	2.5	2.5	2.5	2.5
4	Purified water	5.0	5.0	5.0	5.0	5.0	50	5.0	5.0	5.0	5.0
Extragranular											
5	Sodium starch glycolate	3.5	4.5	5.0	5.0	5.0	5.0	5.0	5.5	6.0	6.5
6	Lactose monohydrate	13.5	13.5	13.5	13.5	13.5	13.5	13.5	13.5	13.5	13.5
7	Magnesium stearate	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
8	Total	85									

Table No.2: Pre-formulation studies

S.No	Trail	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
	Ingredient	**% Composition mg/tablet**									
1	Pioglitazone hydrochloride	33.07	33.07	33.07	33.07	33.07	33.07	33.07	33.07	33.07	33.07
2	Lactose(pharmatose200 m)	42.06	42.06	42.06	42.06	42.06	42.06	42.06	42.06	42.06	42.06
3	Croscarmelose sodium	4.0	6.0	7.0	8.0	8.5	9.0	9.0	9.0	9.0	9.0
Binder											
4	Hydroxypropyl cellulose	9.0	9.0	8.0	7.0	7.0	6.5	6.0	5.5	5.0	4.5
5	Purified water	27.33	27.33	27.33	27.33	27.33	27.33	27.33	27.33	27.33	27.33
Lubrication											
6	Carboxy methyl cellulose calcium	6.66	6.66	6.66	6.66	6.66	6.66	6.66	6.66	6.66	6.66
7	Magnesium stearate	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
8	Total	120									

Table No.3

S.No	Particle size	% cum. Retention
1	40#	6.0
2	60#	11.2
3	80#	14.0
4	100#	15.2
5	200#	18.0
6	325#	22.8
7	Pan	77.2

Table No.4

S.No	Angle of repose (a) degrees	Flow
1	< 25	Excellent
2	25-30	Good
3	30-40 *	Passable
4	40 and above	Very poor

Table No.5

S.No	Compressibility Description	Flow
1	5-15	Excellent
2	12-16	Good
3	18-21	Fair
4	23-28	Poor
5	28-35	Poor
6	35-38	Very poor
7	>40	extremely poor

Table No.6

S.No	Hausner's ratio	Type of flow
1	Less than 1.25	Good flows
2	1.25-1.5	Moderate flow
3	More than 1.5	Poor flows

Table No.7: Information of APIs

S.No	Parametre	Pioglitazone Hydrochloride	Glimepiride
1	Name of the material	Pioglitazone hydrochloride	Glimepiride
2	Synonyms	Pioglitazone hydrochloride	glimepiride
3	Chemical name	(±)-5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-thiazolidinedione monohydrochloride	1-[[p-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)ethyl]phenyl] sulfonyl]-3-(trans-4-methylcyclohexyl) urea
4	Molecular formula	C19H20N2O3S•HCl	C24H34N4O5S
5	Molecular weight	392.90	490.62
6	Solubility	Soluble in N, N-dimethylformamide, slightly soluble in anhydrous ethanol, very slightly soluble in acetone and acetonitrile, practically insoluble in water and insoluble in ether.	Soluble in dimethylsulfoxide, slightly soluble in acetone, very slightly soluble in acetonitrile and methanol and practically insoluble in water.

Physical property of API

Table No.8

S.No	Parameter	Pioglitazone Hydrochloride	Glimepiride
1	Description	Pioglitazone hydrochloride is an odorless, white crystalline powder.	Glimepiride is a white to yellowish-white crystalline, odorless to practically odorless powder.
2	Bulk density Untapped Tapped	0.342g/ml 0.568g/ml	0.316g/ml 0.555g/ml
3	Partical size	% cum Retention	% cum Retention
	40#	0.0	15.7
	60#	2.7	21.2
	100#	13.7	33.3
	200#	34.1	69.0
	325#	59.6	97.3
	Pan	40.4	2.7

Parameters of pioglitazone Granules

Table No.9

S.No	Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	Moisture content	2.42	2.32	2.15	2.11	2.04	1.94	1.67	1.47	1.35	1.30	1.23	1.17
2	Bulk density- Untapped	0.420	0.472	0.554	0.531	0.516	0.527	0.533	0.543	0.531	0.549	0.592	0.586
	Tapped	0.582	0.621	0.685	0.666	0.651	0.660	0.651	0.649	0.632	0.649	0.697	0.694
3	Compressibility index	28	24	19.2	20.2	20.8	20.3	18.2	16.3	16.1	15.4	15.4	15.6
4	Hausner ratio	1.38	1.31	1.23	1.25	1.26	1.25	1.22	1.20	1.19	1.18	1.17	1.18
5	Sieve analysis	% cumulative retention											
6	20#	37.7	35.6	30.2	17.2	24.2	18.9	19.7	25.6	19.9	17.8	15.4	14.4
7	40#	65.2	61.7	58.8	37.9	59.5	46.2	53.2	58.2	42.2	45.3	43.4	42.5
8	60#	76.3	74.8	75.8	59.3	73.7	73.2	70.5	72.7	60.5	60.2	58.7	57.5
9	100#	87.2	86.4	85.6	80.1	82.4	82.3	81.6	81.1	80.9	81.8	79.2	75.0
10	200#	92.3	90.8	90.4	90.9	89.1	92.7	90.5	87.8	91.7	90.4	89.8	87.9
11	Pan	7.7	9.2	9.6	9.1	10.9	7.3	10.5	12.2	8.3	9.6	10.2	12.1

Parameters of Glimepiride granules

Table No.10

S.No	Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	Moisture content	3.68	1.58	1.94	1.94	3.45	3.72	3.34	3.42	3.41	3.43	3.45	3.44
2	Bulk density untapped	0.453	0.419	0.386	0.327	0.371	0.369	0.353	0.387	0.393	0.386	0.399	0.374
	Tapped	0.574	0.609	0.555	0.454	0.438	0.424	0.412	0.459	0.462	0.453	0.467	0.436
3	Compressibility index	21.2	31.2	30.5	28.1	15.3	13.2	14.5	15.8	15.1	14.8	14.6	14.2
4	Hausner ratio	1.26	1.45	1.43	1.38	1.18	1.14	1.16	1.18	1.17	1.17	1.17	1.16
5	Sieve analysis	% cumulative retention											
6	20#	31.0	1.0	4.2	5.5	3.0	6.7	3.2	4.1	3.5	4.5	3.4	3.1
7	30#	46.5	7.0	12.5	10.8	30.0	45.8	25.8	36.2	32.4	37.1	32.3	30.2
8	40#	67.2	23.0	41.6	51.0	55.0	64.7	50.1	57.3	53.1	59.4	52.3	50.6
9	80#	94.5	57.0	62.1	66	82.0	90.5	86.5	86.3	89.5	87.5	84.7	83.1
10	Pan	5.5	43	37.9	34	18.0	9.5	13.5	13.7	10.1	12.5	15.3	16.9

Parameters of Uncoated Tablet

Table No.11

S.No	Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	Average weight of tablets	205.7	206.5	206.2	205.9	205.7	206	205.8	205.5	205.4	205.9	205.3	205.4
2	Thickness -(mm)	4.02-4.05	4.09-5.0	4.07-409	4.05-4.08	4.06-4.09	5.0-5.5	4.05-4.07	4.04-4.07	4.02-4.05	4.05-4.09	4.07-5.0	4.05-4.06
3	Hardness (Kp)	5.3	5.7	5.5	5.4	5.3	5.9	5.2	5.4	5.7	5.8	5.7	5.6
4	Disintegration time-(min.sec).	4.50	4.20	3.15	3.00	2.30	2.50	2.15	2.05	2.00	1.58	1.57	1.56
5	Friability (%)	0	0.20	0.21	0.19	0.12	0.05	0.19	0.14	0.10	0.10	0.14	0.16

CONCLUSION

The primary mechanism of action of glimepiride in lowering blood glucose appears to be dependent on stimulating the release of insulin from functioning pancreatic beta cells. In addition, extra pancreatic effects may also play a role in the activity of sulfonylureas such as glimepiride. This is supported by both preclinical and clinical studies demonstrating that glimepiride administration can lead to increased sensitivity of peripheral tissues to insulin. These findings are consistent with the results of a long-term, randomized and placebo-controlled trial in which glimepiride therapy improved postprandial insulin/C-peptide responses and overall glycemic control without producing clinically meaningful increases in fasting insulin/C-peptide levels.

At the present efforts are directed towards the formulation development of bilayer dosage form for antidiabetic drugs. During the phase of investigation various factor likely to affect the performance of the bilayer apparatus are felt necessary to be discussed in light of sound theoretical knowledge. Dissolution rate, intrinsic solubility, particle size of the drug, hardness, thickness, friability found to be critical during granulation are some of the factors found to be critical during the development based on the experimental findings.

ACKNOWLEDGEMENT

The authors wish to express their sincere gratitude to Department of Pharmaceutics, Vishwa Bharathi College of Pharmaceutical Sciences, Perecherla, Guntur, Andhra Pradesh, India for providing necessary facilities to carry out this research work.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

BIBLIOGRAPHY

1. Who expert committee on specifications for pharmaceutical preparations, *WHO Technical Report Series,* Thirty-Ninth Report, 929, 2004, 1-152.
2. Snehal Khedkar. Practical problems in developing FDCs and Bilayer tablets in WHO/FIP training workshop hyatt regency hotel sahar airport road, *Andheri East, Mumbai,* 2008, 1-33.
3. Jan Vogeleer, Paul D E Sme. Bi-layer tablets-why special technology is required, *GEA,* 2002, 1-7.
4. Russell Plank, Merck and Co. Challenges of multi-layer compression for combination products, *In AAPS Workshop on Fixed Dose Combination Products,* 2006.
5. Birringer N, Shoemaker S, Gilman C, Haynes M and Plank R. Measurement and optimization of layer adhesion in bi-layer tablets, *In American Association of Pharmaceutical Scientists Annual Meeting, Nashville,* 2005.
6. Leon Lackman, Herbert A. Liberman, Joseph Kaing L. The theory and practice of industrial pharmacy, *W Cat,* 3rd Edition, 1991, 303-310.
7. Michele Danish and Macy Kotthe, In, Gilbert S Banker and Chirstopher T. Rhodes. Mordern pharmaceutics, *Marcel Dekker, Inc, New-York,* 3rd Edition, 1996, 830-840.
8. Robert L. Barkin, Timothy R. Stephen Bruehl. Management of chronic pain, *In Disease a Month Part II,* 42(8), 1996, 461.
9. Robert A. Swarm M D, Menelaos Karanikolas M D, Rahul Rastogi M B, B S and Myint Maw, M B, B S, M P H. Pharmacological options for low back pain, *In Semin Pain Med,* 2, 2004, 175-185.
10. Podczeck F, Drake K R, Newton J M, Harian I. The strength of bi layered tablet, *Europian Journal of Pharmaceutical Sciences,* 29(5), 2007, 361-366.
11. Lauretta Maggi, Evelyn Ochoa Machisste, Maria Lusia Torre, Ubaldo Conte. Formulation of biphasic release tablet containing slightly soluble drug, *Europian J of Phar and Bio,* 48(1), 1999, 37-42.
12. Chuan-yu Wu, Jonathan Seville P K. A comparative study of compaction property of binary and bi layer tablet, *Powder Technology,* 189(2), 2009, 285-294.
13. Narendra C, Srinath M S and Ganesh Babu. Optimization of bi layer floating tablet containing metoprolol tartrate as a model drug for gastic retention, *AAPS Pharmsci Tech,* 7(2), 2006, e23-e29.

14. Shirwaikar A A, Srinatha A. Sustain release bi-layer tablets of diltiazem hydrochloride using insoluble matrix system, *Indian Journal of Pharmaceutical Science,* 66(4), 2004, 433-437.
15. Girish S. Sonar, Devendra K. Jain, Dhanajay M. More Preparation and *in vitro* evaluation of bi layer andfloating-bioadhesive tablets of rosiglitazone maleate, *Asian Journal of Pharmaceutical Sciences,* 2(4), 2007, 161-169.
16. Uhmwangho M U and Okar R S. Modification of Drug Release from pioglitazone granules by Melt granulation technique consideration of release kinetics, *Pak. J. Pharm. Sci,* 19(1), 2006, 22-27.
17. Qing-Ri Cao, Yun-Woong Choi, Jing-Hao Cui, Beom-Jin Lee. Formulation, Release characteristics and bioavailability of novel monolithic hydroxy propyl methyl cellulose matrix tablets containing pioglitazone, *In Journal of Controlled Release,* 108(2-3), 2005, 351-361.

Please cite this article in press as: Sunil Mekala *et al*. Formulation development and *in-vitro* evaluation of bi-layered immediate release tablets of pioglitazone and glimepiride, *Asian Journal of Research in Biological and Pharmaceutical Sciences,* 9(1), 2021, 19-26.