FORMULATION OF METFORMIN HYDROCHLORIDE LAYER BY DIRECT COMPRESSION METHOD

Dr. J. PRASANNA KUMARI
Associate Professor,
Department of lndustrial Pharmacy and Pharmaceutics,
Vijaya College of Pharmacy, Hyderabad.

Abstract:
Bilayered tablets of antidiabetic agents are formulated and evaluated in the research work. Preformulation studies of drug and excipients are also carried out. A bilayered tablet was developed for metformin and glimepiride with a view of intended use for immediate and better relief in case of patients having insulin independent diabetes. The results and discussion described under different headings as follows.

Introduction

Preformulation studies

science of the properties of compounds (Candidate drugs). Before starting prototype Formulation of metformin-glimepiride bilayer tablets, reformulation studies for both metformin and glimepiride pure drugs are performed. Following are results of reformulation studies carried out for metformin and glimepiride pure drug, which were methods, explained.

Organoleptic studies of metformin and glimepiride (color, odor and taste)

Metformin and glimepiride were found to have followed organoleptic characteristics.

Organoleptic studies of metformin (color, odor and taste) Color: White crystalline powder.

Odor: None. Taste: Slight bitter.

Organoleptic studies of glimepiride (color, odor and taste):

Color: white to yellowish white. Odor: None.

Taste: None.

Drug – Excipient's compatibility study

Moisture content:

Many medication varying quantities of plain water in the kind of drinking water of crystallization i.e., hydration or consumed kind. It is thus crucial to define the constraints of water material as a way to keep up some type of uniformity from these medications.

Glimepiride and excipients compatibility data is shown in tables 12 and 13. Three parameters, color, moisture content and impurities are observed after one month storage. In all cases there were no color change was observed on physical observation. The increase in moisture content along with the excipients after one month storage is below 13 % w/w except in case of povidone. Glimepiride with povidone after period of one month moisture content observed was 17.16 % w/w.

The presence of impurities after one month stage drug along with excipients was observed by HPLC. In all cases the impurities level is well below 3 % w/w. However, in case of glimepiride with aerosil percentage of impurities was 3.28 % w/w which is beyond the limit. Therefore, aerosil in combination with glimepiride was excluded in further formulation.

Table - Preformulation of glimepiride along with its excipients

Test	**Results**		
		At 40° C, 75 % *RH*	
	Zero day	**After two weeks**	**After one month**
	Glimepiride		

Moisture content	0.22 %	.1 %	.32 %
Total impurities	0.80 %	1.0 %	1.0 %
	Glimepiride with M.C.C PH 102(Avicel PH 102)		
Moisture content	5.32 % w/w	5.47 % w/w	6.36 % w/w
Total impurities	1.03 %	1.26 %	1.67 %
Glimepiride with lactose monohydrate			
Moisture content	5.19 % w/w	5.04 % w/w	5.19 % w/w
Total impurities	0.94 %	0.93 %	1.06 %
Glimepiride with maize starch			
Moisture content	10.13 % w/w	11.33 % w/w	13.09 % w/w
Total impurities	0.77 %	0.85 %	1.16 %
Glimepiride with sodium starch glycolate			
Moisture content	4.87 % w/w	7.52 % w/w	11.78 % w/w
Total impurities	0.77 %	0.83 %	1.0 %
Glimepiride with Ac-Di-Sol			
Moisture content	3.38 % w/w	6.96 %	9.66 %
Total impurities	0.80 %	0.83 %	1.00 %
Glimepiride with povidone			
Moisture content	8.04 % w/w	13.02 %w/w	17.16 % w/w
Total impurities	0.80 %	0.82 %	1.00 %
Glimepiride with magnesium stearate			
Moisture content	1.83 %	1.83 %	5.79 %
Total impurities	0.81 %	0.81 %	1.02 %
Glimepiride with aerosol			
Moisture content	0.89 %	1.26 %	0.91 %
Total impurities	1.19 %	2.16 %	3.28 %
Glimepiride with iron oxide yellow			
Moisture content	0.26 %	.50 %	.27 %
Total impurities	0.84 %	0.96 %	1.0 %
Glimepiride with lake of sunset yellow			
Moisture content	1.01 %	01.16 %	01.23 %
Total impurities	0.76 %	0.98 %	0.90 %

Table - Preformulation of glimepiride along with its excipients

Test	**Results**		
		At 40° C , 75 % *RH*	
	Zero day	**After two weeks**	**After one month**
Glimepiride with HPC-*lf*			
Moisture content	4.29 %	4.88 %	5.79 %
Total impurities	0.74 %	0.82 %	1.02 %

Fourier transforms infrared spectroscopy

As explained in the methodology department that the Fourier transform infra-red conducted with medication metformin-glimepiride together with their preferred excipients. The Outcomes have been outlined as follows.

Metformin hydrochloride.

pure metformin, metformin mixed with HPMC, and metformin mixed with HCO are shown in Figure (fig.-08) to (fig.-10), respectively.

An pure metformin A peak 3371.56 cm^{-1} – Free NH_2 group

Another peak at 1625.41 cm^{-1} – C=NH

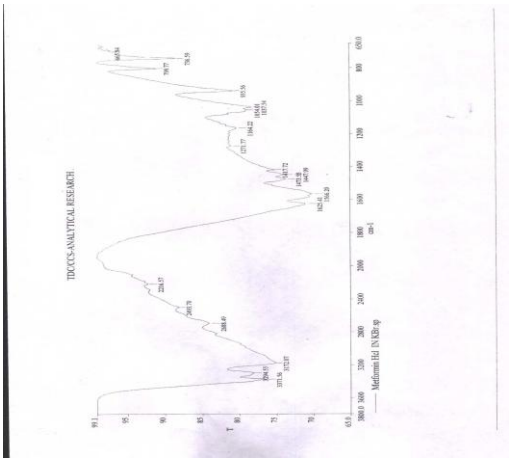
The above two metformin. two are case of metformin excipients HPMC HCO as shown in Figure (fig.-08) to (fig.-10) and Table 6.3 gives the interpretation data.

Table - Wave number of functional groups of metformin along with excipients

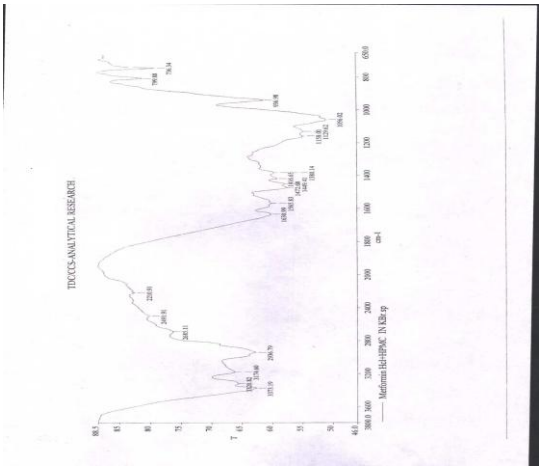
Functional groups	Pure metformin (Figure 08)	Metformin + HPMC (Figure 09)	Metformin + HCO (Figure 10)

Free NH_2 group	3371.56 cm^{-1}	3373.19 cm^{-1}	3371.69 cm^{-1}
C=NH	1625.41 cm^{-1}	1630.99 cm^{-1}	1627.37 cm^{-1}

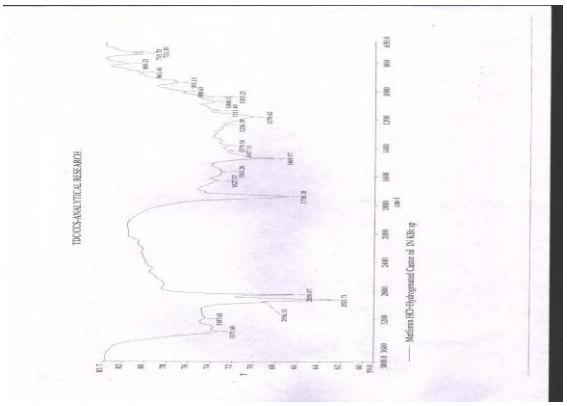
Therefore, perusal to Figure (fig.08) to (fig.10) indicates metformin and HCO). these two excipients are selected as release retardant agents.



Graph - I.R-spectra of pure Metformin hydrochloride



Graph 6.2 I.R Spectra of Metformin with HPMC



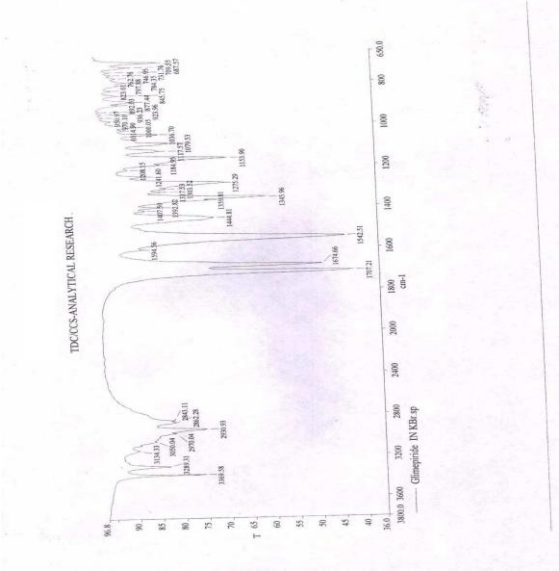
Graph - I.R Spectra of Metformin with Hydrogenated castor oil

Glimepiride

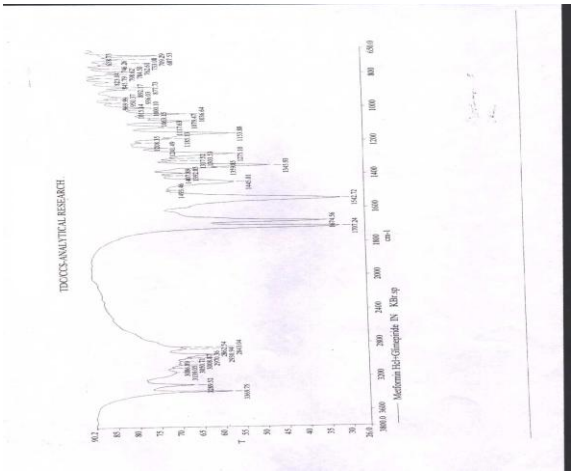
IR spectra of pure glimepiride, glimepiride mixed with metformin are shown in Figures 11 and figure 12, respectively.
glimepiride.
3369.58 cm-N-H stretching of secondary sulphonamide (3390 to 3330 cm^{-1}). Three bands due to ring stretching vibrations in the region of 1600 to 1300 cm^{-1} in case of pyrrole.
A peak at 1444.81 cm^{-1} - substituted cyclohexane.
Above mentioned two peaks and a band for glimepiride. band are also observed in case of IR spectra of glimepiride with metformin mixture the 15 -11 -12

Table - Wave number of functional groups of glimepirides along with physical mixture

Functional groups	Pure glimepiride (Figure 11)	Glimepiride + metformin (Figure 12)
Secondary amine	3369.58 cm^{-1}	3369.75 cm^{-1}
Pyrrole ring	3 bands at 1600 to 1300 cm^{-1}	3 bands at 1600 to 1300 cm^{-1}
Substituted cyclohexane	1444.81 cm^{-1}	1445.01 cm^{-1}



Graph 6.4 I R. Spectra of pure Glimepiride



Graph 6.5. I R Spectra of Metformin hydrochloride with glimepiride

Therefore, perusal to figures 11 and 12 glimepiride- metformin glimepiride and its. Hence, these two drugs metformin and glimepiride are selected for, metformin sustained release and glimepiride immediate release bilayer tablets.

Solubility studies

Solubility of metformin and glimepiride in various solvents was checked qualitatively and broadly classified solubility of metformin and glimepiride in various solvents and different pH solutions as described in the methodology. Depending on the saturation solubility data as discussed in the methodology the dissolution media selected for metformin and glimepiride are buffer solutions pH 6.8 and pH 7.8 respectively.

6.4. Analytical Methods

Metformin hydrochloride

Suitable analytical method was developed for metformin hydrochloride with ultra violet spectrophotometer a wavelength of 233 nm was identified presence of solution, is constructed in this medium. The method has shown reproducibility with R^2 value 0.9999. aliquot of from two micro gram to ten micro gram per milliliters pH 6.8 phosphate buffer for metformin

6.5 Glimepiride: Chromatographic conditions (HPLC)

Mobile phase: Triethylamine (7.0 ml) is taken and mixed with water of100ml then pH is adjusted by adding dilute orthophosphric acid to pH three. Solution of triethylamine (pH 3.0) and acetonitrile were mixed in 50:50 v/v and degassed.

Flow : 1.0 ml/minute
Temperature : Ambient Load : 20 µl
Runtime : 12 min
Λmax-Wave length : 226 nm.

6.6 Formulation of bilayered tablets

As explained in the methodology phase that the bilayered pills were geared up for metformin manual compression way is employed and also for glimepiride moist granulation way can be employed. In event there is metformin coating, most of excipients and active pharmaceutical substances mixed, taken for compression right back. Whereas in event there is glimepiride coating soaked granulation by the addition of the excipients equally intra and added granularly. Various polymers had been utilized in various doses to find good stretch-controlled discharge of medication, gives similar medication

discharge of this promoted solution and gave very excellent f-1 along with f-2 values. Various excipients are utilised, i.e., lead compressible excipients, lubricants, and glidants.

Powder characteristics like angle of repose was determined and given:

Table 6.5**,** gives the values determines property of flow for final blend or granules.

Table 6.5 Flow properties for different values of angle of repose were given below

Tan Ɵ values	Flow
More than 25	Flow property is excellent
Between 25 to 30	Flow property is Good
From 30 to 40	Moderate (addition of 0.2% glidant required)
> 40	Poor

6.7 For compressibility index:

The compressibility index is to determine flow of granules. The detailed compressibility index values are given in below table 6.6.

Table 6.6 Percentage compressibility index

Limits	Nature
From 5 to 12	Free flowing nature
From 12 to 16	Good enough
From 18 to 21	Fair enough
From 23 to 35	Poor flow

Houser's Ratio: it gives values which explains the flow property of granules or blend, the values are given in table 6.7

Table 6.7 Hauser,s Ratio

Sl.No	Hauser's proportions	Nature of flow
1.	1.2	Free flowing
2.	1.3-1.6	Cohesive powder

6.8 Manufacture of metformin and glimepiride bilayered tablets

Metformin-Glimepiride bilayered tablets were prepared using 27 station bilayer compression machines. Metformin tablets are manufactured in direct compression process, granules of glimepiride prepared by traditional granulation technique were placed over the metformin tablet and compressed to get bilayered tablet. Formulas for metformin hydrochloride layer with various excipients are given in table 6.7. And their physical characterization and evaluation results are given in table – 6.8

Table 6.8 Formulation of metformin layer from Formulation 1 to 5

Ingredients	**Quantity per tablet (mg)**				
	Formulation1	**Formulation2**	**Formulation3**	**Formulation4**	**Formulation 5**
Merformin	500	500	500	500	500
HCO	311	321			
HPMC K 100M			210	280	270
PVP K 90D	25	25	85	85	85
MCC			150	80	90
Magnesium steareate	4	4	5	5	5
TW	840	850	950	950	950

The physical properties of metformin from Formulation 1 to 5 were shown Table 6.9.

The results of parameters (LBD, TBD, compressibility) are satisfactory.

Table 6.9 In Vitro release of metformin from Formulations 1 & 2 containing HCO as drug retarding agent

Time in hours	*Cumulative percent of drug release, AM □ SD	
	Formulation 1	Formulation 2
0	0	0
2	40 □1.0	49 □1.0
4	52 □1.0	62 □ 2.0
8	90 □2.0	81 □ 1.5
12	97 □1.0	95 □ 1.0

After optimizing Formulation 2 for metformin layer, an attempt was made to give coating around metformin layer of Formulation 2 by coating solution containing glimepiride. Ingredients for coating of glimepiride layer given in table.

Table - The formula used to prepare coating solution containing glimepiride

Sl.No	Glimepiride coating solution	
	Ingredients	Mg per tablet
1.	Opadry pink	19.89
2.	Glimepiride	2.00
3.	Polysorbate 80	0.11
4.	Purified water	q.s

After completion of coating process coated tablet were subjected for physical evaluation and for estimation of content uniformity. The surfaces of coated tablets were rough, moreover blisters were observed on the surface of the tablets. The content uniformity was 105, 107, 105 and 102 respectively. The content uniformity of the glimepiride was not satisfactory. Therefore, the idea of glimepiride over metformin layer was dropped in further trials.

To prepare glimepiride granules of Formulation 8 this is shown in Table 6.11, excipients are as follows. Lactose and MCC114 are selected as intergranular agents, cross povidone was added as disintegrant, and PVP K 90 D is added as binder. Polysorbate 80 as surfactant for increase the solubility of glimepiride added in formulation. Whereas MCC 102, flowlac and cross povidone were added extragranularly as diluent and disintegrant respectively. Lake of sunset yellow was used as coloring agent and the lubricant used was magnesium steatrate.

The physical properties of glimepiride from Formulation 8 to 14 were shown Table 6.12 and the results of parameters (LBD, TBD, tan Ɵ, compressibility) are satisfactory.

Table - Drug release percent of Formulation 8

Time in min	*Cumulative percent of drug release AM □ SD Formulation 8
0	0
10	27□1.0
15	45□0.5
30	57□1.5
45	69□1.0

Table 6.13 In Vitro release of metformin from Formulations 03 to 05 containing HPMC K 100M

Time in hours	*Cumulative percent of drug release,		
	F-3	F-4	F-5.
0	0	0	0
2	37□1.0	49□1.0	40□1.0
4	60□1.0	64□1.5	66□1.0
8	95□2.0	81□1.5	82□1.5
12	98□1.0	93□1.0	102□1.0

*Determinations value average of six

Formulation 6 was an attempt to coat Formulation 5, in which coating solution contains glimepiride as per formula mention in Table 6.10 and this formula was discarded due to the formation of blisters on the coated tablets.

Metformin granules obtained by wet granulation of Formulation 5 and glimepiride granules Formulation 8 were compressed to get bilayered tablets. This bilayered (i.e., Formulation 5 along with Formulation 8) considered as Formulation 5 of metformin blend was optimized, therefore, for compression of bilayered tablets; this is kept constant along with varying glimpiride blends come across further sections.

Table - Cumulative percent of glimepiride release in case of Formulation 9

Time in min	**ımulative percent of drug release of Formulation 9 AM □ SD**
0	0
10	45□1.0
15	75□1.0
30	89□1.5
45	105□0.5

*Each value was determinations of six average values

Table - Cumulative percent of glimepiride release of Formulation 10 and Amaryl

Time in min	**Cumulative percent of drug release (AM □ SD)**	
	Formulation 10	**Amaryl**
0	0	0
10	37□1.0	97□1.0
15	50□1.5	98□1.5
30	89□2.0	97□1.0
45	95□1.0	99□1.0

*Each value was determinations of six average values

Table 6.11 revels that the release profile of glimepirde of Formulaiton 10 was consistence with USP specification (95 percent in 45 minutes), however release of glimepiride from Formulation 10 was not matching with innovator product.

0	0	0
10	93□1.0	97□1.0
15	97□1.0	98□1.5
30	98□2.0	97□1.0
45	99□1.0	99□1.0

*Each determination is value was an average of six

.Details of ingredients and weights of reproducible batch 01 of both metformin (Formulation 5) and glimepiride (Formulation 14) are shown in Table 30. The compressed tablets of batch 01 conducted drug release studies. The drug release rate both drugs was compared with innovator products Glucophage (for metformin) and Amaryl (for glimepiride). The results are shown in Table 6.17 and Figures 19 and 20

Table - Optimized and reproducible batch 01 of metformin and glimepiride

Metformin blend (Formulation 5)			**Glimepiride blend(Formulation 14)**		
Sl.No	Ingredients	Mg/tablet	Sl.No	Ingredients	Mg/tablet
1.	Metformin Hydrochloride	500.00	1.	Glimepiride	2.00
2.	HPMC K 100 M	240.00	2.	Mannitol	62.00
3.	PVP K 90 D Bp	60.00	3.	MCC 114	97.00
4.	PVP K 90 D BP	25.00	4.	S S G	10.00

5.	IPA	q.s	5.	Poloxamer	3.00
6.	Purified water	Required. quantity	6.	Purified water	Required.quantity
7.	MCC 102	90.00	7.	HPC-LF	5.00
8.	HPMC K 100 M	30.00	8.	Meglumine	3.00
9.	Magnesium Stearate	5.00	9.	MCC102	50.00
Total weight		950.00	10.	S.S.G.	6.00
			11.	Lake of Sunset yellow ws	0.50
			12.	Magnesium Stearate	1.50
			Total weight		240.00

Table - Cumulative percent of metformin release in Formulation 15 and 16

ime in min	*Cumulative percent of drug release AM □ SD		
	Formulation 15	Formulation 16	Formulation 17
0	0	0	0
2	52□1.0	45□1.0	46
4	72□1.0	69□1.5	65
8	98□1.0	85□1.0	83
12	98□2.0	97□1.0	98

*Each determination is value of average of six

Tablets obtained from Formulation 16 showed drug release patterns matches with USP specification, the release profile is shown in the Table 34. However, the blend of Formulation 16 could not able to flow easily from hopper to die cavity during compression.

To overcome the flowability problems in Formulation 16, silicon-di-oxide was added in the next Formulation 17. The release profile of which is shown in Table 34 and also compared with innovator product, which was matching and hence Formulation 17 was optimized for metformin by direct compression.

Further reproducibility Batch 02 0f bilayered tablets were produced by compressing both metformin layer (Formulation 17) and glimepiride layer (Formulation 14) using bilayer compression machine. Details of ingredients and weights of batch 02 of both metformin and glimepiride are shown in Table 35. The compressed solid dosage form tablet from batch-2 conducted drug release studies. Details of batch 02 and its physicochemical properties are given in Table 36. Drug release from both layers of batch 02 as shown in table 39 is within the specification of USP limits and matching with the innovator products. The comparison of dissolution of drug release is shown in Table 6.23 and Photo of in house developed bilayer tablets of metformin and glimipride of batch 02 are shown.

Table - Optimized reproducible batch 02 of metformin and glimepiride

Metformin blend			Glimepiride blend		
Sl.No	Ingredients	mg per tablet	Sl.No	Ingredients	mg per tablet
1.	Metformin Hydrochloride	500.00	1.	Glimepiride	2.00
2.	HPMC K 100 M	360.00	2.	Mannitol	62.00
3.	MCC 102	140.00	3.	MCC 114	97
4.	silicon dioxide	5	4.	S S G	10
5.	Mg. Stearate	4.5	5.	Poloxamer	3.00
Total weight		1010.00	6.	Purified water	q.s
			7.	HPC-LF	5.00

	8.	Meglumine	3.00
	9.	MCC114	50.00
	10.	S S G	6.00
	11.	Lake of Sunset yellows	0.50
	12.	Magnesium Stearate	1.50
	Total weight		240.00

Table - Physical properties of metformin and glimepiride blends in batch 02

Parameters	Metformin hydrochloride	Glimepiride
LBD, mg/cc	0.4615	0.5656
TBD, mg/cc	0.5987	0.6991
Angle of repose	19.12	21.98
Compressibility, %	22.91	19.09
Drug content, %	97	100
Uniformity of weight, mg	1010□5	240 □10

Table - Comparison of dissolution profiles of batch 02 of Formulation 17

*Cumulative percent of drug release AM □ SD					
T-min	nulative release of glimepiride		T-hours	nulative release of metformin	
	Formulation 19	Amaryl		Formulation 19	Glucophage
0	0	0	0	0	0
10	92	97	2	45	43
15	97	98	4	62	59
30	99	97	8	82	83
45	101	99	12	100	103
*Each determination is value of average of six					
F2=76.44 & F1=2.55				F2=79.26 & F1=3.12	

Physical evaluation of bilayered tablets: prepared tablets are evaluated according to the procedure given in methodology for weight variation, friability, thickness and hardness. The results of physical evaluation of bilayered tables of different formulation are given in following table – 38 and table – 39

Table - Physical characteristics of Formulation 2 and 5 of glimepiride coated metformin tablets

Formulation No.	Weight variation (mg)	Friability (%) **	Hardness (KP) *	Thickness (mm) *
F-2	840-858	0.002	24.8-28.4	6.5-6.8
F- 5	941-958	0.004	26.3-31.5	6.4-6.9

*Each determination is value of average of six

Table - Physical characteristics of Formulation 4 to Formulation 17 (bilayered Tablets)

F-No.	Weight variation(mg)*	Friability (%)**	Hardness (KP/cm^2)*	Thickness (mm)*
F-6	963-974	NA	NA	6.6-6.9
F-7	988-995	NA	NA	6.8-7.1
F-8	1145-1168	0.0054	18.5-21.4	7.45-7.75
F-9	1139-1158	0.004	17-20.4	7.36-7.68

F-10	1139-1165	0.0024	19-25.6	7.24-7.55
F-11	1137-1161	0.0012	16.6-22.4	7.45-7.79
F-12	1141-1158	0.0014	17.5-25.4	7.49-7.89
F-13	1175-1199	0.0036	22.6-28.2	7.48-7.78
F-14	1188-1195	0.0014	27.5-30.5	6.91-7.32
F-15	1185-1198	0.0025	25.4-29.2	7.12-7.32
F-16	1181-1192	0.0012	24.8-29.4	7.51-7.62
F-17	1175-1193	0.0016	23.6-29.4	7.62-7.72
F-18	1220-1270	0.0025	28.4-32.8	6.91-7.22
F-19	1230-1262	0.0017	27-34.8	6.8-7.14

*****Each determination is value of average of six ** one batch results

Determination of granules size (average granule size): granules of metformin hydrochloride and glimepiride of optimized batch were taken for particle size determination according to the procedure mentioned in methodology. The results obtained are given in following table.

Optimize blends of metformin (Formulation 05) and glimepiride (Formulation 15) are subjected for weight distribution analysis. The data is shown in Table 6.26 and 6.27

Average granule size was found 447.87 µ m, which is calculated as below.

Average diameter of particle = Σ (nd) / Σ (n)

= 44456.2 / 99.26

= 447.87 µm.

Average granules size of Formulation 14 (glimepiride blend) was found 284.01 µ m, which was calculated as below. A graphical representation of weight distribution of the granules of Formulation 14 was shown in Table 41 and Figure 26

Average diameter of particle = Σ (nd) / Σ (n)

= 28097.7/ 98.93

= 284.01µm.

Effect of Different Parameters on Drug Release

According to methodology, the Medication release Account at Various States was Contrasted with All Conventional profile Launch of Medication to Check on Various parameters of Ingredients That Were Active Discharge.

Effect of hardness of the Tablets:

To be able to validate aftereffect of hardness drug discharge dissolution reports were ran on tablet computers using three distinct sorts of hardness (8 kp/cm2," 10 kp/cm2 and also 12kp/cm2). Additional parameters of these pills continue being exact very identical. Pills of hardness ended up shot for medication launch studies as well as also the outcomes have been all awarded as dining table arrangement dining table forty two and also a chart is plotted at the Figure 27. The accumulative proportion of metformin published in 1-2 hours," was ninety nine, 98, along with 85 present to Pills together for example 8, 10, and 1-2 kp/cm2 hardness, and respectively. When in comparison to pills of 8 kp/cm2 hardness, the dissolution account of pills 10kp/cm2 has been diminished. Likewise, compared to pills of 10 kp/cm2 hardness, the diminished medication discharge had found from 1 2 kp/cm2 hardness pills.

Conclusion

The floating, instantaneous and bi-layer pills were compacted with 9.5 M M, 4mm,

9.5M M curved horizontal faced cries with RIMEK I multi-purpose channel inkjet hitting device. It's quickly absorbed in using of roughly 3 3% also a removal halflife which range from 1.5 to 2.5h. Hydrochlorothiazide is a thiazide diuretic which also is traditionally used from the treating moderate to moderate hypertension. It's very slightly soluble in warm water using plasma halflife of 6h into 14h. For formula of bi-layer floating pills drifting in addition to instantaneous re lease layers had been optimized individually. Crospovidone and also Indion 4 14 were utilized as superb disintegrant. Ethyl cellulose utilized being a bouyoncy enhancer and discharge retardant. Fourier transform infra red spectroscopy and DSC thermograms affirmed lack of almost any drug/polymers/excipient's interactions. Hence an endeavor was built to improve oral bioavailability of both Losartan and Hydrochlorothiazide adjusted dose blend by simply keeping the dose kind in gut to get lengthier time period. That really is accomplished by growing gastroprotective drifting medication shipping procedure. These pills were well prepared to improve the bioavailability of these medication using the medication to entire scope preventing pointless frequency of dosing and then first raise metabolism. Immediate compression procedure has been utilized to invent the pills, as a result of its cost efficacy and thanks to decrease quantity of fabricating ways. The geared up drifting pill computer, instantaneous launch pill computer and bi-layer pills are assessed for hardness, fat variant, depth, friability, medication material uniformity, at vitro disintegration period, buoyancy lag period, complete suspended period and drinking water uptake (inflammation indicator), Inviter dissolution scientific reports. All formulas were exposed to five distinct designs viz. Zero arrangement, original arrangement, version specimens most of closely version.

References:

1. *Amin P. Indion 414 as Superdisintegrant in Formulation of Mouth Dissolve Tablets. Ind J Pharm Sci. 2011; IP: 59.92.253.166*
2. *Anilkumar J. Shinde, Arun N. Waghule, Manoj B. Paithane, Harinath N. More. formulation and in vitro evaluation of sustained release floating tablet ofcephalexin using hydrophilic polymers. Int J of Pharmacy and Pharma Sci 2010; 2 (2): 58-65.*
3. *Arora S, Ali J, Ahuja A, Khar RK, Baboota S. Floating drug delivery Systems: a review. AAPS PharmSciTech. 2005; 6(3):E372-E389.*
4. *Aryal S, Skalo BN. Stability of amlodipine besylate and atenolol in multi-component tablets of mono-layer and bi-layer types. Acta Pharm. 2008; 58:299-308.*
5. *Available from URL: http://en.wikipedia.org/wiki/losartan*
6. *Available from URL: http://www.merck.com/product/usa/pi_circulars/c/cozaar*
7. *Available from URL: http://www.tsrlink.com.*
8. *Brijesh S Dave, Avani E Amin, Madhabai M Patel. Gastroretentive drug delivery system of ranitidine HCl: Formulation and in vitro evaluation. AAPS Pharm Sci Tech. 2004; 5 (2) Article 34.*
9. *Chawla G, Gupta P, Bansal AK. Gastroretentive drug delivery systems. In: NK Jain, editor. Progress in controlled and novel drug delivery systems. New Delhi (India): CBS; 2004, p.79-80.*
10. *Chena RN, Ho HO, Yu CY, Sheu MT. Development of swelling/ floating gastroretentive drug delivery system based on a combination of hydroxyethyl cellulose and sodium carboxymethyl cellulose for losartan and its clinical relevance in healthy volunteers with CYP2C9 polymorphism. Eur J Pharm Sci 2010; 39:83-9.*
11. *Chena RN, Ho HO, Yu CY, Sheu MT. Development of swelling/ floating gastroretentive drug delivery system based on a combination of hydroxyethyl cellulose and sodium carboxymethyl cellulose for losartan and its clinical relevance in healthy volunteers with CYP2C9 polymorphism. Eur J Pharm Sci. 2010; 39:83-9.*