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Pharmaceutical Sciences **RESEARCH ARTICLE……!!!**

DEVELOPMENT AND EVALUATION OF BI-LAYERED TABLETS CONTAINING VALSARTAN AS IMMEDIATE RELEASE AND METFORMIN AS SUSTAINED RELEASE: A NOVEL APPROACH TO INCREASE THERAPEUTIC EFFICACY

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KEYWORDS:

Valsartan, Metformin Hydrochloride, Hydroxy Propyl Methyl Cellulose, Cross Carmellose, Sodium Starch Glycolate.

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ABSTRACT

The objective of the present study is to formulate a fixed dose combined drug formulation of valsartan (VAL) as an immediate release layer and metformin HCl (MHCl) as a sustained release form using bilayer tablet technology, which enables biphasic drug release for once daily dosing to get a better therapeutic efficacy. The immediate release layer was prepared using super disintegrant cross carmellose and extended release layer using xanthum gum., hydroxy propyl methyl cellulose(HPMC K15) and Povidone K90. The physicochemical compatibility and stability of the tablets were determined by Fourier transform infrared spectroscopy (FTIR). Bilayer tablets were subjected to accelerated stability studies for 6 months. The *in-vitro* release hardness, friability, weight variation, thickness, and drug content uniformity and subjected to *in vitro* drug release studies using different kinetic models. The amount of VAL and MHCl released at different time intervals were estimated by UV Spectrophotometer. FTIR, data for the formulations indicate good compatibility and stability. These tablets exhibit no significant change either in physical appearance or dissolution pattern after storage at accelerated condition (40±2°C / 75±5%RH) for 6 months. The results indicated that VAL and MHCl could be a potential fixed dose combination form for the simultaneous treatment of hypertension and diabetes and can be developed into suitable bilayer tablets.

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INTRODUCTION:

Hypertension is extremely a common situation in diabetes patients. Diabetes generally increases the risk of developing high blood pressure and other cardiovascular problems, because it adversely affects the arteries, predisposing them to atherosclerosis which is well known as hardening of the arteries (Sowers JR, Epstein M and Frohlich ED, 2001; Epstein M and Sowers JR, 1992). Now a day's fixed-dosed combination are getting accepted because of simplified treatment regimens, superior clinical effectiveness, better patient adherence and economical (Pimenta E and Oparil S, 2008). For fixed dose combination products, bilayer tablets are commonly prepared with one layer of drug for immediate release while second layer designed to release drug, later, either as second dose or in an extended release manner for biphasic release of two different drugs in combination which improves patient compliance and prolongs the drug action (Nagaraju R and Kaza R, 2009; Podczeck F, Drake KR, Neton JM and Harian I, 2006). VAL is a nonpeptide, angiotensin II receptor antagonist with particular high affinity for type 1 (AT1) angiotensin receptor. It acts as a vasoconstrictor which also stimulates the synthesis and release of aldosterone, blockage of its effects results in a decrease in systemic vascular resistance, hence used for the treatment of hypertension (Budavari S, ONeil MJ, Smith A and Heckelman PE, 2001). MHCl is a biguanide glucose lowering agent that has been widely used for management of noninsulin dependent diabetes mellitus (NIDDM) (Dunn CJ and Peters DH, 1995; Bailey C, Path M and Turner M, 1996). MHCl therapy is suboptimal as it is associated with a high frequency of dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery, so sustained release matrix formulation dosage form was developed which provide a better control of plasma drug levels, less dosage frequency leading to diminished side effects, increase efficacy and constant delivery with cost effective (Verma RK, Mishra B and Garg S, 2000; Mukherjee B, Dinda SC and Barik BB, 2008; Dinda SC and Mukherjee B, Samanta A, 2011).

Hydroxypropylmethylcellulose, hydrophilic matrices was used for sustained release drug delivery which is previously suitably investigated for its use as retardant for modifying the drug release rate (Mukherjee B, Dinda SC and Barik BB, 2008; Babu GVMM, Prasad DS, Himasankar K, Gourisankar V, Kumar NK and MurthyVR, 2002; Rao YM and Javasagar JKG, 2001; Yan G, Zhang R and Ding D, 2000; Cao QR, Chai YW, Cui JH and Lee BJ, 2005; Reddy S, Kumar PP, Rajanarayana K, Rao YM, 2010).

MATERIALS AND METHODS:

VAL and MHCL were received as a gift from Granules India, Hyderabad, Aurbindo labs ,Hyderabad India. Hydroxy propyl methyl cellulose (HPMC K100M) was donated from chemika-Biochemika-Reagents (OTTO), Mumbai India. Microcrystalline cellulose (Avicel pH 101) and

sodium carboxy methyl cellulose was obtained as gift sample from Chemika-Biochemika-Reagents(OTTO), Mumbai. Magnesium stearate from Chemika-Biochemika-Reagents(OTTO), Mumbai. All other reagents used were of analytical or pharmaceutical grade.

Fabrication of bilayer tablet:

Fabrication of bilayer tablets followed direct compression and wet granulation technique for both immediate release VAL layer and sustained release MHCl layer. For formation of immediate release layer accurately weighed quantity of VAL,cross carmellose, sodium starch glycolate microcrystalline cellulose(Avicel PH101), were screened using screen #25. The screened powders were then transferred into the mixer and mixed for 10 min. Magnesium stearate was sifted through #40 screen and added to the above powder mix and mixed for 3 min at 20 rpm.

For formation of sustained release layer MHCl sustained release tablet wet granulation method involves sifting of drug along with the polymers and diluents like sodium CMC, hydroxyl propyl methyl cellulose,xanthum gum,povidone k30, were passed through sieve # 80 and uniform mixing was carried out for 5 minutes. Granulation was performed by using PVP K30 as a binder and Isopropyl alcohol as a solvent to form dough mass. The mass was passed through sieve No.18 and the granules so prepared were dried at25-27^{0}C for 2 hrs. Afterwards granules were sized through sieve # 18. Finally magnesium stearate and Talc were added separately and mixed for further 2-3 minutes.

Evaluation of Granules:

Angle of repose is a relatively simple technique for estimation of the flow property of a powder. Powders with low angle of repose are free flowing and those with a high angle of repose are poorly flowing powders.10 gm of granules were passed through funnel and the pile was formed. The height and weight of the pile was measured and the angle of repose was calculated by using the formula:-

Angle of repose (θ) = tan-1 (h/r)

The Carr's compressibility index was calculated by calculating the tapped and bulk density using the 100 ml measuring cylinder. Compressibility is calculated by the formula,

$$C= 100\times (1- \rho B)/ \rho T$$

Where ρB is the freely settled bulk density of the powder, and ρT Hausner's Ratio is the tapped bulk density of the powder. A Carr's index greater than 25 is considered to be an indication and poor flowability, and below 15, of good flow ability.

Hausner's ratio was related to interparticle friction and could be used to predict powder flow properties. Hausner's values of the prepared granules ranged from 1.12 to 1.25 were thought to indicate good flow properties.

$$\text{Carr's index (\%)} = [(TD-BD) \times 100] / TD$$

Hausner's ratio = TD / BD

Compression of bilayer tablets:

Compression of bilayer tablets were done by using Cadmach double rotary bi-layer compression machine (Cadmach, India). The prepared granules of each layer were compressed using 19.00× 9.00mm, 'D' tooling standard concave, flat faced modified capsule shaped punch. The hardness was kept between 10-15kp. Both the prepared granules came from two different hoppers to two different feed frames where they occupied the die cavity. The bottom or first layer of MHCL was compressed first with lower pressure, which was then followed by filling of the die cavity by the second layer VAL. The final compression was done only after both the granules occupied the die cavity one on top of the other. Both the layers were identified on the basis of colour since the immediate release layer had red colour and the sustain release layer is white colour.

Determination of uniformity of weight : Twenty (20) tablets from each batch were independently weighed by an analytical balance. The average weight, standard deviation and relative standard deviation were recorded. The tablet compression machine was suitably in tune to produce tablets of uniform weight (IPC, 2007).

Determination of thickness of the tablet:

The thickness in millimetres was measured individually for 10 preweighed tablets by using a starrett portable dial hand micrometer. The average thickness, standard deviation and relative standard deviation were reported (IPC, 2007, Vidyadhara S, Rao PR, Prasad JA, 2006).

Determination of hardness of the tablet:

Tablet hardness was measured using electrolab hardness tester. The crushing strength of the 10 tablets with known weight and thickness of each was recorded in kilopond (kp) and the average hardness, standard deviations, and relative standard deviations were reported. Tablets hardness was checked at the start and during the compression process to control an acceptable range of tablet hardness (IPC, 2007, Vidyadhara S, Rao PR, Prasad JA, 2006).

Determination of friability of the tablet:

Twenty (20) tablets were selected from each batch and weighed. Each group of tablets were rotated at 25 rpm for 4 min (100 rotations) in the electrolab tablet friabilator. The tablets were then will dust and re-weighed to determine the loss in weight. Friability was then calculated as percent weight loss from the original tablets (IPC, 2007, Vidyadhara S, Rao PR, Prasad JA, 2006).

Determination of uniformity of dosage units:

This was assessed according to the USP requirements for content uniformity. The batch meets the USP requirements; ten tablets of VAL and MHCl were powdered separately and the blend equivalent to 80mg of VAL and 125mg of MHCl respectively were weighed and dissolved in

suitable quantity of phosphate buffer of pH 6.8. The solutions were filtered separately and suitably diluted. The drug content was analysed by UV at 233nm for MHCl and at 271nm for VAL. The amount of the active ingredient in each of the 10 tested tablets lies within the range of 95% to 105% of the label claim and the RSD is less than 5% (IPC, 2007, Vidyadhara S, Rao PR, Prasad JA, 2006).

In vitro drug release test:

In-vitro drug release study for the bi-layer tablets was conducted by using a six-station USP XXVII type II apparatus (Electrolab Tablet dissolution tester USP, TDT-06P). VAL was analysed at 37 ± 0.5°C, Apparatus II (paddle), using 900ml phosphate buffer (pH = 6.8) as the dissolution medium and at a rotation speed of 50 rpm. Aliquots, each of 5ml, from the dissolution medium were withdrawn after 5, 10, 15, 30, 45 and 60 min and replaced by an equal volume of fresh dissolution medium. After filtration through whatman filter paper, the sample solution was analyzed by using). MHCl was analysed as per USP dissolution (711), at 37 ± 0.5°C, apparatus II (paddle), at a rotation speed of 100 rpm using 0.1 N HCl , 900ml for 0 to 2h and in phosphate buffer (pH = 6.8) for remaining 16h. Aliquots, each of 5ml, from the dissolution medium were withdrawn after 1, 2, 3, 4, 6, 8, 10, 12, and 16h and replaced by an equal volume of fresh dissolution medium. After filtration through whatman filter paper, the sample solution was analyzed by using UV at 233nm. A minimum of 3 tablets per batch were tested and the results were taken as average of three test reading with standard deviations. The amount of drug present in the samples was calculated with the help of appropriate calibration curve constructed from reference standard. Further, the in-vitro drug release studies for the marketed tablets (Diovan 80mg for VAL and Glucophage XR 500mg for MHCl) were conducted (J.W. Moore, H.H. Flanner, 1996, The U. S. pharmacopoeial Convention, 2002).

In-vitro drug release kinetics:

In order to study the accurate mechanism of drug release from the matrix layer of MHCL, drug release data was analyzed according to zero order, First order, Hixon-Crowell and Peppas kinetic equation. The decisive factor for selecting the most appropriate model was selected on the basis of goodness-of-fit test (t-test).

Accelerated stability studies:

Bilayer tablets were packed in 40cc, air-tight high density polyethylene bottles with 30 tablets in each bottle and then sealed. The bottles were kept in duplicate at 40±2 °C/75±5 %RH for 1, 3 and 6 months. Tablets were evaluated for stability by determining invitro release profile, drug content (self life t90), FTIR studies.

FTIR spectroscopy: Drug-excipients interactions, initial tablets and accelerated condition tablets were carried by FTIR spectroscopy. About 2mg of sample was mixed thoroughly with 200 mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3

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minutes. The resultant disc was mounted in a suitable holder in Perkin Elmer IR spectrophotometer and the IR spectrum was recorded from 4000 per cm to 450 per cm. The resultant spectra were compared for any spectral changes (Dinda SC, Mukerjee B, Damodharan N, Barik BB, 2008)

Table 1: Composition of Metformin hydrochloride sustained release layer

S.NO	Ingredients (in mg)	MHCL 001	MHCL 002	MHCL 003	MHCL 004	MHCL 005
1.	Metformin hydrochloride	500	500	500	500	500
2.	HPMC K15M	120	-	240	-	60
3.	HPMC 1LAKH	-	120	-	240	60
4.	Xantham gum	100	100	-	-	100
5.	Sodium CMC	50	50	50	50	50
6.	Magnesium stearate	10	10	10	10	10

Table 2: Composition of Valsartan immediate release layer.

Ingredients	VAL001	VAL002	VAL003	VAL004	VAL005	VAL006
Valsartan	80	80	80	80	80	80
Sodium starch Glycolate	-	-	-	30	40	50
Cross carmellose sodium	30	40	50	-	-	-
Micro crystalline cellulose	20	30	40	20	30	40
Magnesium stearate	1	1	1	1	1	1
Aerosil	1	1	1	1	1	1

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Table 3: Post compression study for Valsartan IR layer

Batch No.	Thickness (mm)*	Hardness * (kg/cm^2)	Friability* (%)*	Average weight* (mg)	Weight variation*
VAL001	2.57±0.24	2.44±0.05	0.32	142	0.5%
VAL002	2.57±0.27	2.56±0.17	0.44	147	0.8%
VAL003	2.54±0.21	2.69±0.04	0.36	152	0.4%
VAL004	2.56±0.17	2.65±0.20	0.40	142	0.6%
VAL005	2.53±0.28	2.54±0.22	0.46	147	1.2%
VAL006	2.56±0.24	2.54±0.14	0.39	152	0.5%

Table 4: Pre-compression parameters for Valsartan fast dissolving layer.

Batch code	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's Index (I_C)	Hausner ratio(H_R)	Angel of repose(θ)
VAL001	0.30	0.52	22.5	1.26	30.21
VAL002	0.41	0.56	23.7	1.25	34.23
VAL003	0.38	0.53	21.5	1.33	32.76
VAL004	0.32	0.53	20.8	1.24	28.53
VAL005	0.40	0.54	23.2	1.28	31.42
VAL006	0.42	0.53	24.79	1.32	35.78

Table 5: In-Vitro Dissolution Study of Valsartan I.R Layer

Time (Hours)	% Cumulative Drug Release					
	VAL001	**VAL002**	**VAL003**	**VAL004**	**VAL005**	**VAL006**
2	9.46	8.72	10.84	7.94	**30.85**	46.72
4	24.21	17.61	19.16	20.00	**53.67**	72.94
6	27.21	25.32	28.24	22.46	**73.56**	91.16
8	32.20	31.42	34.66	25.32	**89.62**	96.40
10	40.11	33.07	43.09	43.05	**95.17**	126.92
15	44.84	51.42	61.62	46.20	**99.19**	-
20	51.66	58.56	65.21	50.64	**100.58**	-
25	53.18	73.20	81.24	63.50		
30	57.32	81.14	90.72	69.74		
40	67.20	92.60	96.14	80.80		

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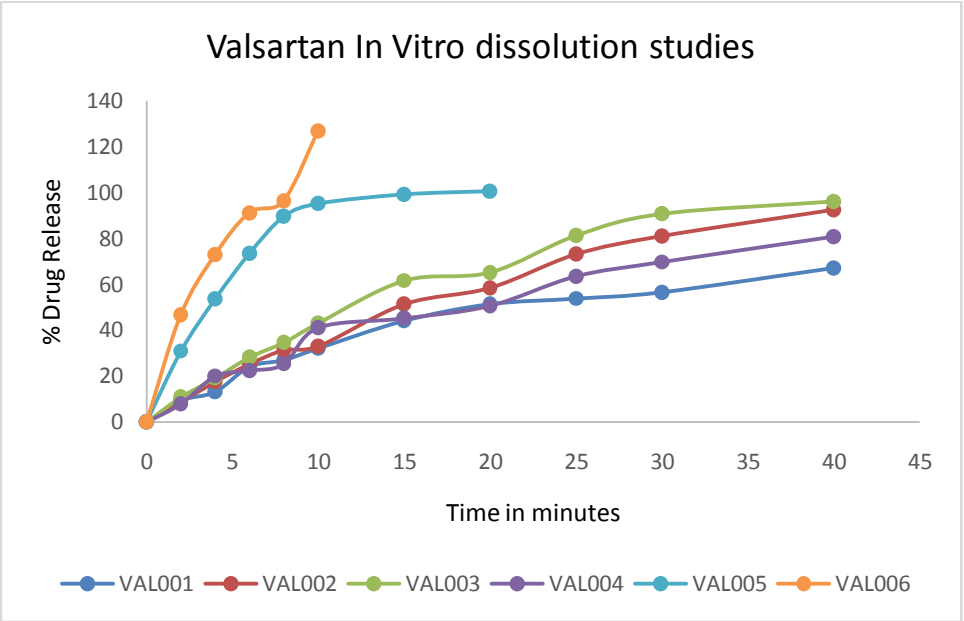

Fig 1: Valsartan In –vitro Dissolution studies

Table 6: Pre-compression parameters for Metformin sustained release layer.

Batch code	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr'sindex (I_C)	Hausner ratio (H_R)	Angel of repose(θ)
MHCL001	0.455 ± 0.29	0.568 ± 0.19	20.8 ±0.13	1.24±0.16	30.1 ±0.28
MHCL002	0.452 ±0.32	0.574± 0.27	21 ± 0.17	1.25±0.17	31.0 ±0.25
MHCL003	0.457 ± 0.39	0.576 ± 0.32	21.4 ±0.23	1.23±0.14	29.8 ±0.23
MHCL004	0.454 ± 0.25	0.552 ± 0.19	20.6 ±0.31	1.26±0.14	30.2 ±0.23
MHCL005	0.451 ± 0.29	0.563 ± 0.14	20.9 ± 0.24	1.23±0.04	31.0 ±0.16

Table 7:In-vitro dissolution profile data of optimized formulations Metformin S.R Layer.

Time (Hours)	% Cumulative Drug Release				
	MHCL001	**MHCL002**	**MHCL003**	**MHCL004**	**MHCL005**
1	20.06	**27.91**	27.24	29.48	25.24
2	45.25	**46.17**	48.88	47.34	41.98
4	60.26	**63.28**	56.90	66.29	57.34
8	78.66	**75. 45**	64.14	86.17	76.59
12	82.10	**88.17**	85.70	98.21	84.26
16	97.05	**100.44**	97.40	-	95.60

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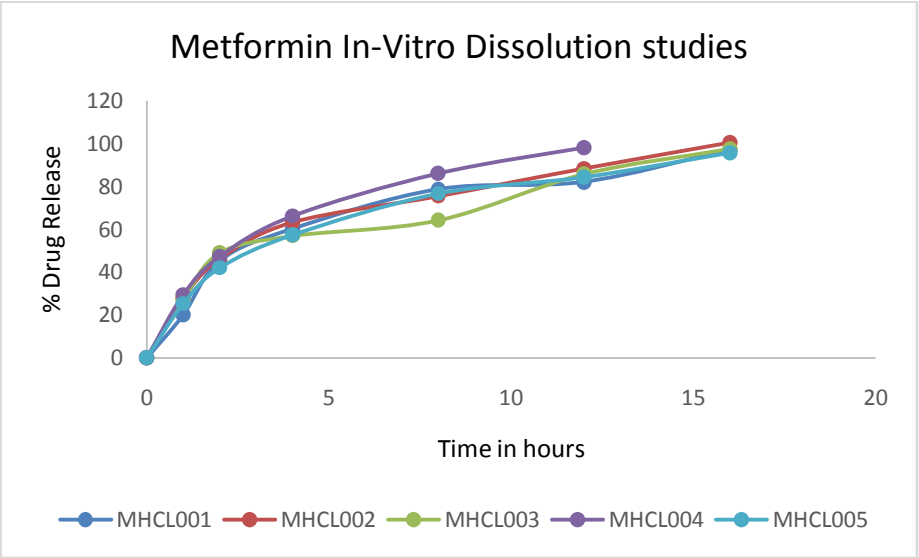

Fig :Metformin In-Vitro Dissolution Studies

Table 8: Post compression parameters of F1-F3 bilayer layer matrix tablet

Batch .No.	Average weight *(mg)	Thickness (mm)*	Hardness* (kg/cm^2)	Friability* (%)*	%Drug Content	
					(MHCL)	(VAL)
F1.	932(0.12)	6.13(0.04)	13.46(0.20)	0.34	100.06(0.01)	99.9(0.92)
F2.	931(0.10)	6.24(0.07)	13.32(0.12)	0.32	99.98(0.19)	99.2(0.98)
F3.	932(0.15)	6.18(0.03)	13.29(0.03)	0.30	99.97(0.89)	97.9(0.89)

Table 9: Physical characters of optimized formulation

Formulation layer	MHCL(M002)	VAL(G005)
Bulk density(g/cc)	0.452	0.401
Tapped density(g/cc)	0.574	0.546
Carr's index(%)	21	23
Hausner ratio	1.25	1.28
Angle of repose(θ)	31	31.4
Flowability	Good	Good

Table 10: In-vitro release study of Bilayer tablets of different formulation.

Immediate Release Layer Valsartan				
S.no	**Time**	**Cumulative % drug release**		
		F1	**F2**	**F3**
1	**45 mins**	92.6	**100.5**	96.1
Sustained Release Layer Metformin Hydrochloride				
2	**1 hr**	20.06	**27.91**	27.24
3	**2 hr**	45.25	**46.17**	48.88
4	**4 hr**	60.26	**63.28**	56.90
5	**8 hr**	78.66	**75.45**	64.14
6	**12 hr**	82.10	**88.17**	85.70
7	**16 hr**	97.05	**100.44**	97.40

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Stability studies :

Table 11: At ambient condition (25±2°C and relative humidity 60± 5%)

Time	Hardness (Kg/cm^2)	Friability (%)	Drug content (%)	Cumulative %drug released at 16 hr
Initial	11.31±0.23	0.52	99.54±0.69	100.25
First Month	11.32±0.29	0.50	99.86±0.8	99.98
Second Month	11.30±0.30	0.53	98.55±0.8	97.44
Third Month	11.32±0.32	0.52	99.05±0.57	98.98

Table 12: At elevated temperature (40±2°C and relative humidity 75± 5%)

Time	Hardness (Kg/cm^2)	Friability (%)	Drug content (%)	Cumulative %drug released at 16 hr
Initial	11.32±0.23	0.52	99.60±0.69	100.17
First Month	11.31±0.29	0.50	99.58±0.8	99.40
Second Month	11.32±0.30	0.54	100.58±0.8	98.44
Third Month	11.34±0.32	0.52	99.65±0.57	99.25

Table 13: Drug release kinetic models fitting optimized formulations

FORMULA	Correlation coefficients(R)			
	ZERO ORDER	**FIRST ORDER**	**HIGUCHI**	**PEPPAS**
F1	0.8254	0.908	0.99	0.930
F2	**0.991**	**0.994**	**0.981**	**0.975**
F3	0.988	0.953	0.983	0.911
F4	0.852	0.953	0.991	0.948
F5	0.957	0.972	0.987	0.972

RESULTS AND DISCUSSION:

MHCl (500mg/dose) sustained release was formulated with matrix technique using the blend of HPMC K 100, HPMC K 15,Xantham gum, sodium carboxy methyl cellulose and poly vinyl pyrrolidone. HPMC in combination with Xantham different formulations M001, M002 , M003.M004,M005 respectively and sodium carboxy methyl cellulose was kept 5% respectively in all formulations (Table 1). The drug release study indicating the drug delivery pattern is sustained up to 16 h, which is appropriate for superior patient compliance (Figure 2). It was observed that drug release of MHCl was notably influenced by sum amount of polymer concentration in the formulation. It was observed in the dissolution study that the drug release HPMC K100 and

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Xantham gum were used which showed a better control of drug release, the drug release were between 29.6% to 31.2% at 1 h (20 to 40%), 50.43% to 50.93% at 3 h (40 to 60%) and 86.79% to 89.76% at 10 h. Hence we can conclude that as per USP, the drug release up to 1 h (20 to 40%), 3 h (40 to 60%) and for 10 h should not be less than 85% was well controlled by the formulation . Drug release of VAL immediate layer was tried with sodium starch glycolate and cross carmellose (Table 2) but predominantly the drug release was best seen with super disintegrant, sodium starch glycolate. VAL was released 75% within 25 min (Figure 1). To describe the kinetics of drug release characterstics (table 13) of the matrix tablets as well as marketed tablets were compared, release data was analysed according to different kinetic equation. It indicates that drug release from the matrix tablets with 20% w/w HPMC K 100 with Xantham gum obeys first order kinetics .Hence it indiactes that the test formulation follows sustained drug release based on first order kinetics and functioned better in controlling the drug release as compared to marketed tablets.

Weight variation, thickness, hardness, friability and uniformity of drug:

All batches pass the weight variation test and found to be within range (930±5%). Thickness variation of bi-layer tablets were also found within limit (5%). Hardness of tablet increases as HPMC amount increase in the first compressed MHCl layer, friability of the tablets ranged from as low as 0.32 (SD±0.08) to as high as 0.38 (±SD 0.50). Friability also decreases as HPMC amount increase. Friability of all batches were found to be well within limit 1% which indicates that tablet surfaces are strong enough to withstand mechanical shock or attrition during storage and transportation and until they are consumed. Drug content of MHCl and VAL in bi-layer tablet in all batches was found within limit (90–110%). The results were represented in Tables 3,4,6 8.

In vitro drug release:

The in vitro drug release of finalized batch data demonstrated that ideally as per USP for MHCl 500mg sustained release tablet, the drug release in 1h should be between 20 to 40%, for 3h should be between 45 to 65% and for 10h should not be less than 85% which was well observed in the in vitro MHCl release. The drug release of MHCl was compared with the innovator tablets, Glucophage XR 500mg. Similarly VAL was released 75% within 45 min. Cumulative % drug release versus time plot for MHCl and VAL were represented in Fig. 1 and Fig. 2 respectively.

FTIR spectroscopy:

The functional group present in the both the drug were identified. The FTIR of MHCl showed intens bands at 3372 cm-1, 1448.81 cm-1 and 1039.77.94 cm-1 corresponding to the functional groups NH, CH3 and CN bending respectively. The FTIR of VAL showed intense bands at 3445.98 cm-1, 2963.28 cm-1, 1730.51 cm-1, 1603.48 cm-1 and 1066.13 cm-1 corresponding to the functional groups NH, C=N, Carboxylate, C=O and CN bending respectively. The wavenumbers of individual drug were compared with final formulated product IR spectrum. The resulted peaks observed in

FTIR are presented in Table No. 5. The FTIR spectra of VAL, MHCl, VAL with excipient mixture, MHCl with excipient mixture were given in Fig. 14, Fig. 15, Fig. 16, and Fig. 17. The results revealed that there was no significant disturbance in the principle peaks of pure drugs of MHCl and VAL. The FTIR spectrum for VAL and excipient mixture reveals a broad peak at 3382.46 cm-1 due to N–H bond stretching. From the interpretation it was understood that there was no major shifting in the frequencies of MHCl and VAL which indicated that there is no chemical interaction in the formulations. This further confirms the integrity of pure drug and compatibility of them with excipients.

STABILITY STUDIES:

Stability studies were carried out on the most satisfactory formulations of F2 for 3 months at 25Š °C/60±5%RH, 30Š °C/65%RH and 40Š °C/75%RH to assess their long term stability as per ICH guidelines Q1C. At the end of 90 days, samples were evaluated. There was no major change in the various physico-chemical parameters evaluated like hardness, drug content and in vitro dissolution pattern.

CONCLUSION:

The results indicated that the optimized bi-layer tablet of MHCl SR and VAL IR could be a potential fixed dose combination form and can be developed into suitable bilayer tablets that are stable and capable of sustaining the drug release. Moreover, the developed product is less complex with regards to formulation components and processing characteristics. These findings could be utilized for various drugs and they may be considered multipurpose in the applications.

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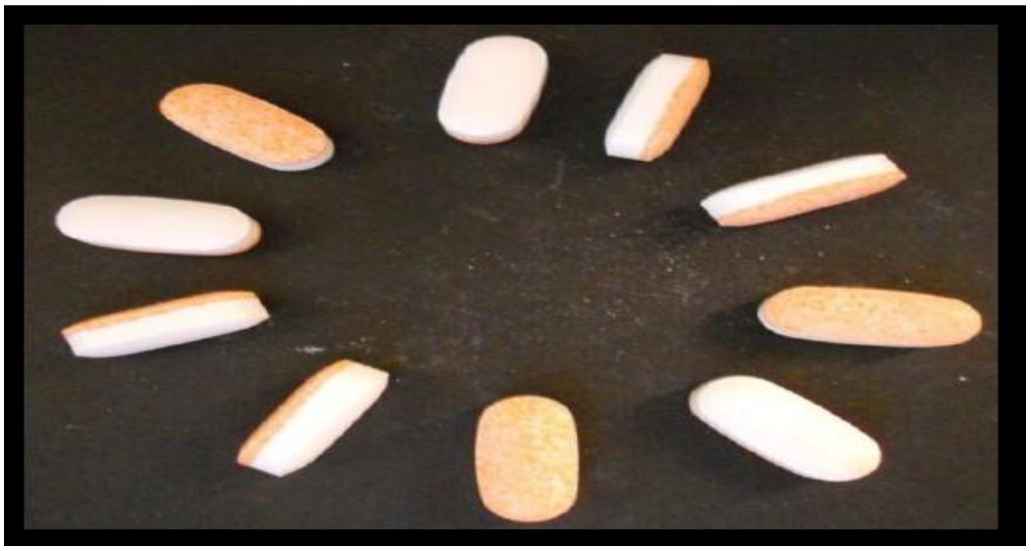

Fig : Photograph of Bilayer tablets