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Formulation and evaluation of bi-layered floating tablets of metformin and telmesartan

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ABSTRACT

The Bilayered tablets containing Metformin and telmisartan were successfully prepared by direct compression method respectively. The physiochemical evaluation results for the powdered blend of all trials pass the official limits in angle of repose, compressibility index. The prepared blend for IR release were also maintained the physiochemical properties of tablets such as thickness, hardness, weight variation, friability. The optimized formulation F5 contains the average thickness of 3.12 average hardness of 4.20, average weight variation of 249, and friability of 0.22. The prepared dry mixer for sustained release tablets were also maintained the physiochemical properties of tablets such as thickness, hardness, weight variation, friability. The optimized formulation F3 contains the average thickness of 6.45 average hardness of 7.6, friability of 0.39. The F3 formulation which releases the Metformin in sustained manner in up to 12 hours and telmisartan immediate release F5 formulation showed 100.6% drug release with in 30min.

Keywords: Angle of repose, Compressibility index and Direct compression method

INTRODUCTION

Tablets

"In 1843, the first patent for a hand operated device used to form a tablet was granted." Tablets are defined as solid preparations each containing a single dose of one or more active ingredients and obtained by compressing uniform volumes of particles. They 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 ingredient "liberated". Tablets are used mainly for systemic drug delivery but also for local drug action. For systemic use drug must be released from tablet that is dissolved in the fluids of mouth, stomach and intestine and then absorbed into systemic circulation by which it reaches its site of action[1]. Tablets remain popular as a dosage form because of the advantages, afforded both to the manufacturer [e.g. simplicity and economy of preparation, stability and convenience in packing, shipping and dispensing] and the patient [e.g. accuracy of dosage, compactness, portability, blandness of taste and ease of administration] [2].

They may differ greatly in size and weight depending on the amount of drug substance present and the intended method of administration[3]. They may have lines or break-marks and may bear a symbol or other markings. Tablets may be coated.

AIM AND OBJECTIVE OF PRESENT STUDY

The aim of the present study was to design and evaluate tablets of metformin and Telmisartan. An attempt was made to develop sustained release tablets suitable for delivering drug with release pattern like as sustained release of drug which gives effect of drug for sufficient long time and reduce frequency of dose[6].

Objectives

1. To optimize the concentration of Polymer for sustaining metformin.
2. To select the suitable filler to produce the bulkiness and desired weight.
3. To select the dissolution media, by performing solubility studies.
4. To perform the drug – excipient compatibility studies as per ICH guideline

METHODOLOGY

Formulation of Immediate release layer

The immediate release granules were prepared by blending the drug with different super disintegrants (Sodiumstarch glycolate, Croscarmellose sodium,Crospovidone) at different concentrations and along with other excipients[4].The granules so obtained were used to obtain immediate release layer of drug in bilayer floating tablets. For preliminary studies to optimize the IR formulations, a weighed quantity of above lubricated drug mixture blend was fed manually into the die and directly compressed using 8 mm flat faced punch of 10 station Cadmach compression machine to get IR tablets. seven formulation batches were made in order to achieve desired disintegration time and drug release[5]. Formulation compositions of different immediate release batches are given in the Table1

Table1: Composition formula for Telmisartan immediate release layer (F1-F7)

Ingredients (mg)	F_1	F_2	F_3	F_4	F_5	F6	F7
Telmisartan	40	40	40	40	40	40	40
Crospovidone	12.5	-	-	25	-	31.25	-
Croscarmellose	-	12.5	-	-	-	-	-
Sodium starch glycolate	-	-	12.5	-	25	-	31.25
PVP	12.5	12.5	12.5	12.5	12.5	12.5	12.5
Magnesium stearate	6.25	6.25	6.25	6.25	6.25	6.25	6.25
Talc	6.25	6.25	6.25	6.25	6.25	6.25	6.25
Micro crystalline cellulose	172.5	172.5	172.5	160	160	153.75	153.75
Total weight	**250**	**250**	**250**	**250**	**250**	**250**	**250**

Formulation of Sustained Release Tablet

The bilayer tablet was prepared by wet granulation method. Sieving: The active ingredient was passed through the sieve#40 followed by the other ingredients were passed the same sieve. Dry mixing: Metformin, guar gum, Dicalcium phosphate (DCP) were taken in a poly bag and mixed for 5minutes to ensure uniform mixing of the ingredients with the drug. Preparation of binder solutionPVP-K_{30}, IPAWeigh PVP K-30 accurately and it is mixed with IPA to form a paste is used as binder solution and kept separately. Granulation: The binder solution was added slowly to the dry mixed ingredients with constant mixing till to get solid mass to form uniform and optimum granules. Drying: Then the wet granules were dried in trays and pass the air for drying since the IPA is corrosive and also get evaporated quickly. So air drying is only suitable for drying, samples were removed randomly at different time intervals from the total bulk of the granules and then checked out for moisture content. Sieving: The dried materials were passed through the sieve#20.After sieving dry granules were lubricated using Mg. stearate. After lubrication granules were sent to compression. Metformin was compressed using 19*9 punch.

Composition of sustained release layer

Table no: 2 formulation table for sustained release layer

Formulation	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8
Metformin	500mg	500mg	500mg	500mg	500mg	500mg	500mg	500mg
Guar gum	190mg	237.5mg	285mg	332.5mg	--	--	--	--
Xanthum gum	--	--	--	--	190mg	237.5mg	285mg	332.5mg
DCP	222mg	174.5mg	127mg	79.5mg	222mg	174.5mg	127mg	79.5mg
Magnesium stearate	9.5mg	9.5mg	9.5mg	9.5mg	9.5mg	9.5mg	9.5mg	9.5mg
PVP K30	28.5mg	28.5mg	28.5mg	28.5mg	28.5mg	28.5mg	28.5mg	28.5mg
IPA	qs	qs	qs	qs	qs	qs	qs	qs
Total weight	950	950	950	950	950	950	950	950

DCP- Dicalcium phosphate, IPA – Iso propyl alcohol, PVP- Poly vinyl pyrrolidine.
All the ingredients are in 'mg'

All the ingredients were passed through sieve and mixed in a motor and pestle for 30min for uniform mixing. The addition of ingredients was done in a geometrical manner.

RESULTS AND DISCUSSION

Preformulation studies

Organoleptic characters for metformin

Colour	White to off white colour

Solubility Parametrs

Freely Soluble	Water
In Soluble	Ether,acetone

Melting point

Melting point of metformin drug was determined by using melting point apparatus and was in the range of 222^0c.

Evaluation of metformin tablets

Table no: 3 Evaluations of pre compression parameters for metformin

Formulations	Angle of Repose (θ)	Loose Bulk Density (g/ml)	Tapped Bulk Density (g/ml)	%Compressibility	Hausner's ratio	Angle of repose
F1	22^0 68'	0.309	0.353	12.46	1.14	Good
F2	25^0 65'	0.321	0.354	9.322034	1.102804	Excellent
F3	25^0 73'	0.318	0.352	9.659091	1.106918	Excellent
F4	24^0 65'	0.510	0.583	12.52	1.14	Good
F5	23^0 73'	0.416	0.482	13.69	1.15	Good
F6	25^0 16'	0.315	0.342	7.894737	1.085714	Excellent
F7	26^0 68'	0.323	0.354	8.757062	1.095975	Excellent
F8	25^0 16'	0.423	0.495	14.54	1.17	Good

From the above pre-compression parameters it was clear evidence that granules has excellent flow properties.

Post Compression Parameters

Tablet No -4Post Compression Parameters for Sustained Release Tablet

F.CODE	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Weight variation
F1	7.5 ±0.44	6.28±0.17	0.32	951±0.12
F2	7.4 ±0.40	6.22±0.17	0.36	952±0.14
F3	7.6±0.31	6.45±0.22	0.39	950±0.02
F4	7.4 ±0.54	6.32±0.27	0.38	950±0.10
F5	7.6 ±0.44	6.26±0.18	0.41	951±0.14
F6	7.5±0.40	6.22±0.80	0.43	950±0.06
F7	7.5±0.55	6.52±0.20	0.12	950±0.04
F8	7.4 ±0.45	6.12±0.22	0.45	950±0.14

Invitro dissolution studies for sr tablets

Dissolution study (sr tablets)

Acidic Stage

Medium : 0.1N HCL
Type of apparatus : USP - II (paddle type)
RPM : 50
Volume : 900ml
Temperature : 37ºC± 0.5
Time : 2hrs

Buffer Stage

Medium : 6.8pH phosphate buffer
Type of apparatus : USP - II (paddle type)
RPM : 50
Volume : 900ml
Time : 8hrs

In vitro dissolution for SR tablets were done initially in 0.1N HCL for 2hrs and next in 6.8 phosphate buffer for 8hrs

In-Vitro Drug Release Studies for SR tablets

Table :5 cumulative percentage drug release of sustained layer

Time	F1	F2	F3	F4	F5	F6	F7	F8
Dissolution medium 0.1N HCL								
1	32.1	29	17	18	58.3	38	33	30
2	48.2	37	28	28	79.6	50	45	51.2
6.8pH phosphate buffer								
3	78.5	49	35	44.2	98.9	65	68	70.9
4	98.2	63	48	55.3		77	80	90.8
5		86	55	70.2		85	97	99.2
6		99.3	73	82.1		91	-	
8		-	87	99.2		-	-	
12		-	98			-	-	

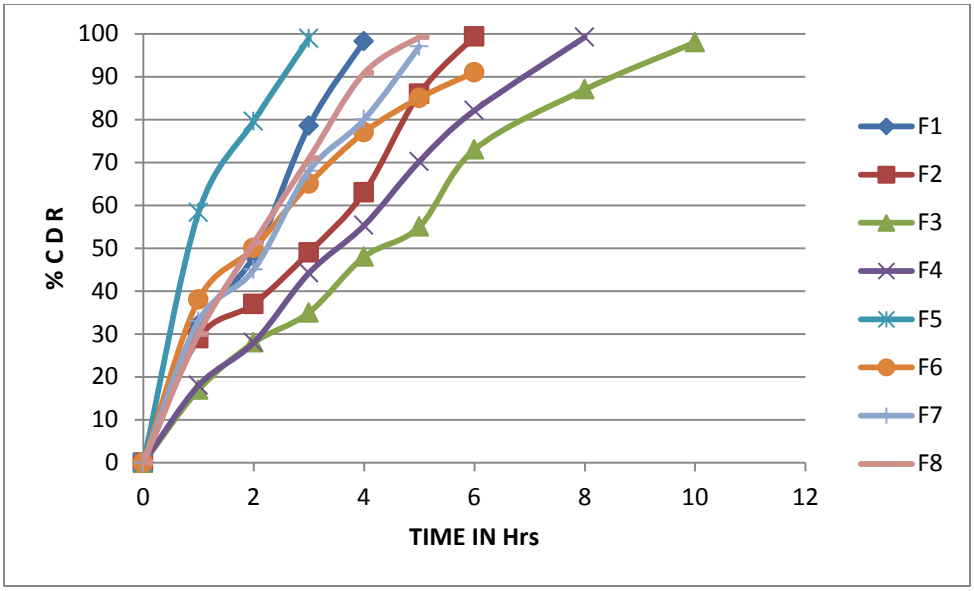

Fig No -1 dissolution graph for sustained release formulations

Kinetic release models

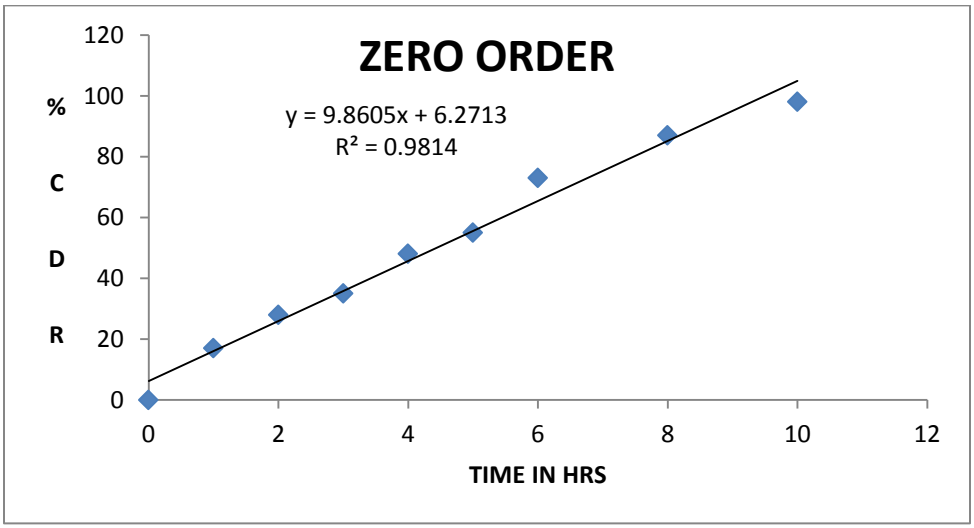

Fig no – 2 zero order release graph for F3 sustained release formulation

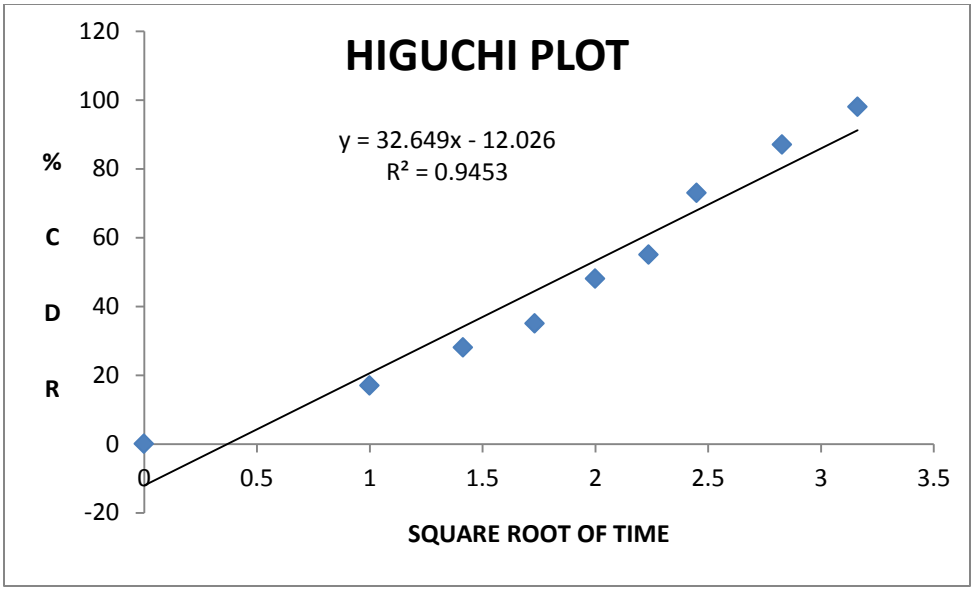

Fig no – 3 Higuchi model graph for F3 sustained release formulation

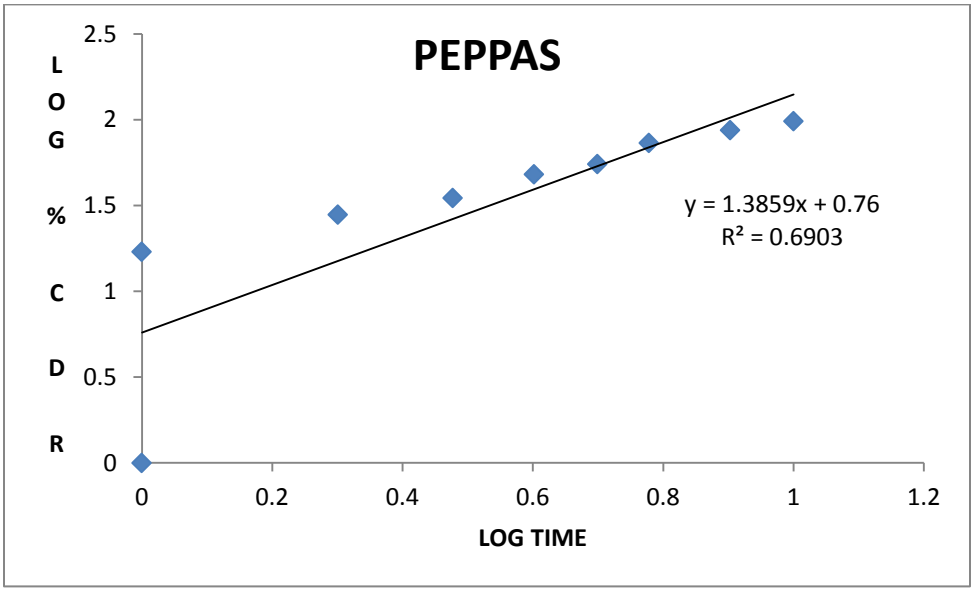

Fig no – 4 peppas model for F3 sustained release formulation

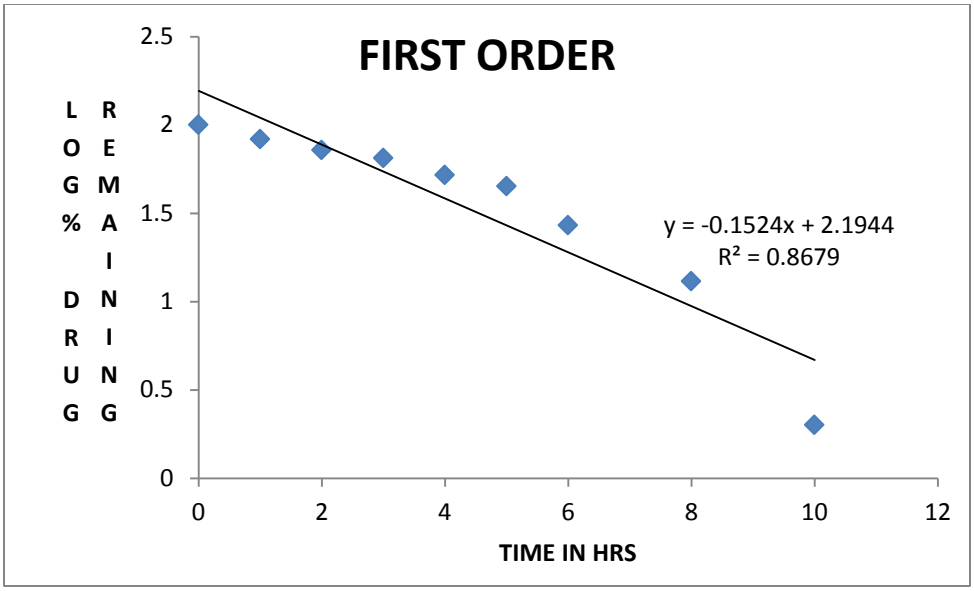

Fig no – 5 First order release graph for F3 sustained release formulation

Table no 6: release kinetics for F3 formulation for sustained release layer

RELEASE KINEITCS				
	ZERO	**HIGUCHI**	**PEPPAS**	**FIRST**
	Q Vs T	Q Vs √T	Log C Vs Log T	Log % Remain Vs T
Slope	9.860	32.64	1.38	-0.15
R 2	0.98	0.94	0.69	0.867

Discussion for *in-vitro* release of metformin

From the table, it was confirmed that the F1,F2, F5, F6, of SR layer does not fulfill the sustained release theory. And also from the table, it was also confirmed that the formulation made with Guar gum (F1,F2,F3 and F4) F3 showed highest percent of drug release compared to the formulations made with XANTHUM GUM (F5 to F8)

Evaluation of telmisartan tablets

Pre-compression parameters for telmisartan blend

The angle of repose of different formulations was found to be in the range of ***24.8 to 28.5.*** Hence this indicates that the material had excellent flow property. The bulk density was found to be in the range of ***0.29 g/cm^3 to 0.45 g/cm^3***. Tapped density was found to be in the range of ***0.34g/cm^3 to 0.52 g/cm^3.*** The Carr's index for all the formulations was found to be in the range of ***12.50 to 20.93.***

Table 7: Characterization of telmisartan Blends

Formulations	**Angle of Repose (θ)**	**Loose Bulk Density (g/ml)**	**Tapped Bulk Density (g/ml)**	**%Compressibility**
F1	24.8	0.3	0.36	16.67
F2	28.5	0.29	0.34	14.71
F3	26.4	0.37	0.45	17.78

F4	27.3	0.34	0.43	20.93
F5	25.2	0.45	0.52	13.46
F6	27.5	0.42	0.48	12.50
F7	25.7	0.34	0.43	20.93

Post compression parameters of telmisartan

Physical characterization of tablets

The thickness of the tablets was found to be in the range of ***3.10-3.28mm***. Hardness was found to be in between ***4.00-4.20Kg/cm^2***. Friability below 1% was an indication of good mechanical resistance of tablets. The formulations showed not more 45min of disintegration time in the prepared batches. All the formulations showed more than 95% of drug content indicating content uniformity in the prepared batches.

Table8: Post compression parameters for immediate release tablets

Formulations	Average weight (mg)	*Hardness Kg/cm^2*	Thickness (mm)	Friability (%)	Disintegration Time	Drug content (%)
F1	256	4.20	3.10	0.18	45 sec	95.8
F2	255	4.00	3.28	0.20	40 sec	99.6
F3	248	4.10	3.20	0.17	45 sec	96.8
F4	247	4.10	3.22	0.16	35 sec	96.8
F5	249	4.20	3.12	0.21	40 sec	99.0
F6	253	4.20	3.11	0.22	40 sec	98.9
F7	258	4.10	3.24	0.18	35 sec	98.4

Invitro dissolution studies

Invitro dissolution studies for telmisartan

In vitro drug release studies were carried out using USP XXIV dissolution apparatus type II, with 900ml of dissolution medium maintained at 37±1°C for 1 hr, at 75 rpm, 0.1 N HCl was used as a dissolution medium. 5ml of sample was withdrawn at predetermined time intervals replacing with an equal quantity of drug free dissolution fluid. The samples withdrawn were filtered through 0.45µ membrane filter, and drug release in each sample was analyzed after suitable dilution by UV/Vis Spectrophotometer at 295nm.

Table No 9: Dissolution for immediate release tablet of Telmisartan

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

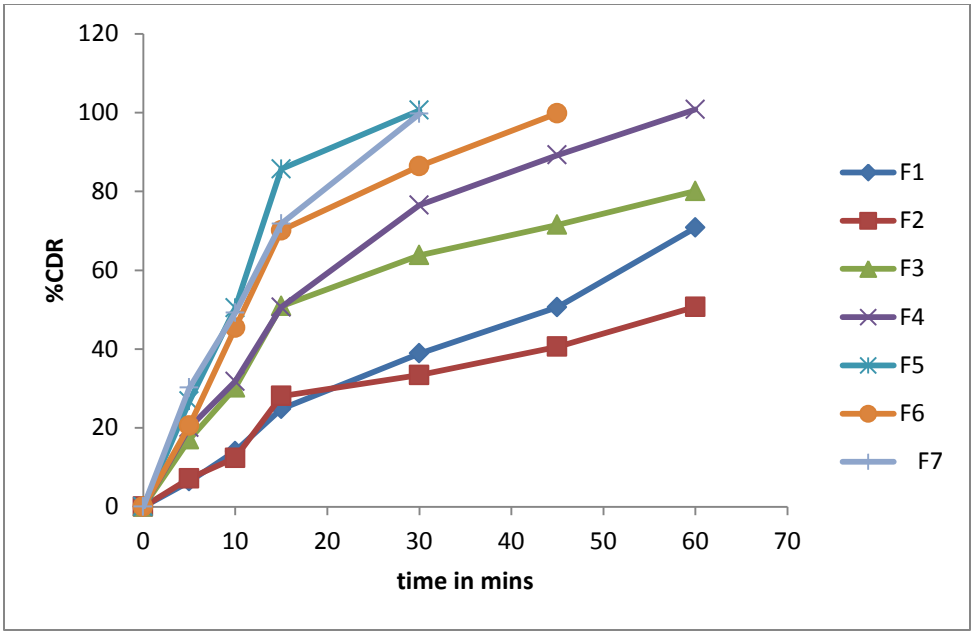

Figure No:6 Dissolution graph for formulations F1-F7

Dissolution study (bilayered tablets)

Table 10 : Dissolution profile of bilayered tablet Metformin(F3) and Telmisartan(F6)

		Percentage drug released (%)	
S.NO	**Sampling time**	**TELMISARTAN**	**METFORMIN**
1	15mins	80.8	3.8
2	30 mins	99.5	8.0
5	1hr	--	29.6
6	2hr	--	33.9
7	3hr	--	42.7
8	4hr	--	55.8
9	5hr	--	65.8
10	6hr	--	77.0
11	8hr	--	89.8
12	12hr	--	98.9

Stability data of optimized formulation

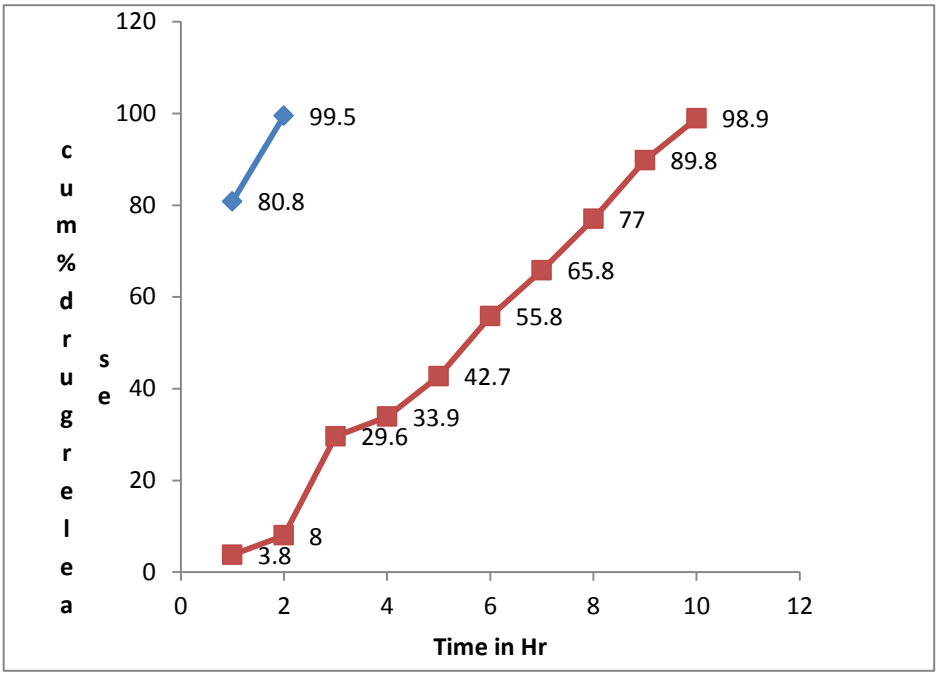

Fig 7: *invitro* dissolution profile for optimized formulation (T1G1

Table no: 11

S.No	Time points (hrs)	Initial	Cumulative % Drug Release (mean ± SD) (n=3)			
			25C/60%RH		40C/75%RH	
			1st Month	3rd Month	1stMonth	3rdMonth
1	0.5	**99.5**	99.4	98.2	98.0	97.7
2	**1**	**29.6**	29.1	28.8	29.5	28.1
3	**2**	**33.9**	33.1	30.0	33.8	32.2
4	**3**	**42.7**	40.2	40.7	43.0	41.6
5	**4**	**55.8**	52.1	51.9	50.5	50.7
6	**5**	**65.8**	65.2	65.1	65.7	64.2
7	**6**	**77.0**	77.1	76.3	76.2	76.1
8	**8**	**89.8**	88.8	87.4	88.4	86.4
9	**12**	**98.9**	97.6	96.9	97.4	96.1

DISCUSSION

The release profile of formulations F_1, F_2, F_3, F_4 F_5,F_6 and F_7 comprising various polymers like crospovidone ,croscarmellose and sodium starch glycolate with equal concentrations. Formulations F_1, F_2, F_3 ,F_4 F_5,F_6 and F_7 exhibits release rates of 70.8%,50.7%,80.1%,100.8%,100.6%,99.8% various time intervals as shown in the table. Among all of these 7 formulations F_5 contains **sodium starch glycolate** shows maximum drug release at the end of 30 mins. Hence it was optimized and decided to develop further formulations.

CONCLUSION

The Bilayered tablets containing Metformin and telmisartan were successfully prepared by direct

compression method respectively. The physiochemical evaluation results for the powdered blend of all trials pass the official limits in angle of repose, compressibility index. The prepared blend for IR release were also maintained the physiochemical properties of tablets such as thickness, hardness, weight variation, friability. The optimized formulation F5 contains the average thickness of 3.12 average hardness of 4.20, average weight variation of 249, friability of 0.22. The prepared dry mixer for sustained release tablets were also maintained the physiochemical properties of tablets such as thickness, hardness, weight variation, friability. The optimized formulation F3 contains the average thickness of 6.45 average hardness of 7.6, friability of 0.39.

REFERENCES

[1]. Reynolds JEF, In; Martindale; The Extra Pharmacopoeia, 29th Edn., The Royal Pharmaceutical Society of Great Britain, London,1993, pp 295.
[2]. Mcnaman JO, Hardman JG, Limbird LE, Molinoff PB and Ruddon RW. Eds., The Pharmacological Basis of Therapeutics: 9th Edn. Mc Graw-Hill.
[3]. Indian Pharmacopoeia. Vol. II, 4th ed. TheController of Publications, New Delhi,1996, p736
[4]. Aithal KS, Udupa N, Ind. J. Pharm. Sci., 1992; pp 255-257.Thakkar VT, Shah PA, Soni TG, Parmar MY, Gohel MC, Gandhi TR. Fabrication and evaluation of levofloxacin hemihydrates floating tablets. Res Pharm Sci 2008; Vol: 3, pg: 1-8.
[5]. Bomma R, Swamy Naidu RA, Yamsani MR, Veerabrahma K. Development and evaluation of gastro retentive norfloxacin tablets. Act. Pharma 2009; Vol: 59: pg: 211-21.
[6]. http://link.springer.com/article/10.1007%2Fs10973-012-2467-3
[7]. AM Raggi; R Mandrioli; A Ferranti; J. Pharm. Biomed. Analysis., 2003, 32, 1037-1044.
[8]. P Colombo; Adv Drug Del Rev., 1993, 11, 37-57
[9]. J Siepmann; H Kranz; R Bodmeier; NA Peppas; Pharm Res., 1999, 16, 1748-1756.
[10]. http://www.dovepress.com/update-on-extended-release-quetiapine-fumarate-in schizophrenia-and-bi-peer-reviewed-article-NDT-recommendation1
[11]. AnilkumarJ. Shinde, Manojkumar S. Patel and Harinath N. Formulation and in vitro evaluation of sustained release floating tablet of Cephalexin using hydrophilic polymers. Int. J. Pharma and Pharmaceutical Sci- 2010, Vol 2.
[12]. Martindale: Thirty first Edition, The Complete Drug Reference. P.102.1