Original Research Article

FORMULATION DEVELOPMENT AND EVALUATION OF BILAYER TABLETS CONTAINING PARACETAMOL SR AND TIZANIDINE

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ABSTRACT

In the present study Paracetamol and Tizanidine were considered as the model drugs for development of bilayer tablets. Paracetamol with the dose 600mg/tablet was considered under the matrix layer and Tizanidine with the dose 2mg/tablet was considered under immediate release layer. The polymers like HPMC (Hydroxy propyl methyl cellulose) K100 & K4 grades, guar gum are used for development of matrix layer. The calibration curve for Paracetamol was plotted by using UV spectroscope at an absorbance of 280 nm as per the method developed by glenmak pharmaceutical ltd. The calibration curve for Tizanidine was plotted by using HPLC at an absorbance of 230nm. The physicochemical parameters of both the matrix tablets of Paracetamol as well as bilayer tablets were carried out. The formulation of sustained release layer was optimized with respect to their dissolution parameters. The dissolution of the bilayer tablets were carried out in 0.1N HCl. The optimized batches showing a release rate more than 90% were considered for development of bilayer tablets. The pharmacokinetic parameters for both the matrix layer formulations of Paracetamol as well as bilayer tablets were conducted with zero order, first order, higuchi and korsemeyer patterns. The optimized formulations were found to be following zero order release kinetics. The accelerated stability study of the optimized formulations (matrix layer and bilayer tablets) were conducted for three months at the conditions of 40^{o}c/75%RH and found to be stable. The FTIR study was conducted for determining drug polymer interaction.

***Keywords*:** Bilayer tablets, HPMC K100 & K4, Guar gum, Paracetamol, Tizanidine.

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1. INTRODUCTION

Conventional dosage forms are accused of repetitive dosing and unpredictable absorption window that cause wide range of fluctuation in drug concentration in the blood stream and tissues with subsequent undesirable toxicity and poor therapeutic efficiency.[1] This dynamic such as repetitive dosing and erratic absorption led to the concept of controlled drug delivery systems. Formulation of layers from different polymers allows manipulation over more than one rate-controlling polymer, thus enabling different types of drug delivery of one or more drugs, i.e. where the drug may be released with a bolus and then at a controlled rate or by targeted drug delivery in the GI tract using pH dependant polymers.[2] The aim in designing sustained or controlled delivery systems is to decrease the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or provide uniform drug delivery. The main objective of sustained release drug delivery is to make sure safety and to improve effectiveness of drugs as well as patient compliance. But often this controlled drug delivery system fails to

achieve the stated advantages due to lack of releasing the initial bolus dose dose dumping and failure to achieve site specific drug delivery.[3] Immediate release drug delivery system is intended to disintegrate rapidly, and exhibit instant drug release. It is associated with fluctuations in drug plasma levels, which leads to reduction or loss in drug effectiveness or increase incidence of side effects. Administration of the DDS several times per day is therefore necessary to compensate the decrease in drug plasma concentration due to metabolism and excretion. A relatively constant plasma level of a drug is often preferred to maintain the drug concentration within the therapeutic window. However, it is difficult to achieve, especially for once-daily dosage forms, partly because the environment for drug diffusion and/or absorption varies along the gastrointestinal (GI) tract. On the basis of these considerations, we have proposed a bilayer tablet.[4, 5]

1.1, Advantages of bilayer technology

- ✓ Bilayer tablets can be designed in such manner as to modify the release as either of the layers can be kept as extended and the other as immediate release.
- ✓ The Bi - layer tablet is suitable for preventing direct contact of two drugs and thus to maximize the efficacy of a combination of two drugs.
- ✓ Separation of incompatible components. Prospective use of single entity feed granules. Greatest chemical and microbial stability over all oral dosage forms. Objectionable odour and bitter taste can be masked by coating technique. Bilayer execution with optional single – layer conversion kit.
- ✓ Low cost compared to all other dosage forms.
- ✓ Offer greatest precision and least content uniformity.
- ✓ Easy to swallow with least hang up problems.
- ✓ Flexible concept.
- ✓ Suitable for large scale production.
- ✓ Lighter and compact. Patient compliance is improved leading to improve drug regimen efficiency.
- ✓ They are a unit dosage form and offer the greatest capabilities of all oral dosage forms for the greatest dose precision and least content variability. Patient compliance is improved fewer daily dose are required compared to the traditional delivery system.

1.2, Reasons for preparing bilayer tablets

- Controlling the delivery rate of either single or two different API'S.
- To separate incompatible API's with each other, to control the release of one layer by utilizing the functional property of the other layer (such as osmotic property).
- For the administration of fixed dose combinations of drugs, Prolong the drug product life cycle**,** vocal/mucoadhesive delivery systems, manufacture novel drug delivery systems such as chewing device and floating tablets for gastro-retentive drug delivery systems.
- To adapt the total surface area available for API layer either by sandwiching with one or two inactive layers in order to achieve swellable / erodible barriers for controlled release.
- Bi-layer tablet is 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. In which the one layer is formulated to obtain the immediate release of the drug, with the aim of reaching a high serum concentration in a short period of time. The second layer is a controlled release, which is designed to maintain an effective plasma level for a prolonged period of time. The pharmacokinetics advantage relies on the fact that drug release from fast releasing layer leads to a sudden rise in the blood concentration. However, the blood level is maintained at a steady state as the drug is released from the sustaining layer.[6]

2. MATERIALS AND METHODS

All the materials used in the study were obtained from Glenmark pharmaceuticals limited, R&D centre, Nasik, India. All the chemicals and reagents used in this study are of analytical grade.

2.1, Development of sustained layer of Paracetamol (matrix layer)

Matrix tablets of Paracetamol were formulated by using three different polymers such as Guar gum, HPMC K4M and HPMC K100M in different concentrations by wet granulation technique using 5-6 % starch paste along with PVP-K30 as a binder.

2.2, Preparation of matrix tablets with Guar gum.

Required quantities of Paracetamol & Luctomann P 5000 (Guar gum) were weighed accurately and then they are blended uniformly. Starch paste (5%) was added to get a damp mass. The damp mass was passed through sieve number 10 to get the granules which are then dried at 50^0C for 30mins in rapid process drying (RPD). The dried granules were further passed through sieve number 16, lubricated with a mixture of magnesium stearate and talc and compressed to obtain tablets using (20.3 X 9.8 mm) Capsule shaped flat punch on Cad mach single punch tablet machine.

2.3, Preparation of matrix tablets with HPMC K 100 M.

Required quantities of Paracetamol & HPMC K 100 M were weighed accurately and blended uniformly. Starch paste (5%) was added to get a damp mass. The damp mass was passed through sieve number 10 to get the granules which are then dried at 50^0C for 30min in rapid process drying (RPD). The dried granules were passed through sieve number 16, lubricated with a mixture of magnesium stearate and talc and compressed to obtain tablets using (20.3 X 9.8 mm) Capsule shaped flat punch on Cad mach single punch tablet machine.

2.4, Preparation of matrix tablets with HPMC K 100 M & HPMC K4 M.

Required quantities of Paracetamol & HPMC K 100 M were weighed accurately and then they are blended uniformly. Then sufficient quantity of 5-6 % starch paste was added to get a damp mass. The damp mass was passed through sieve number 10 to get the granules which are then dried at 50^0C for 30min in rapid process drying (RPD). The dried granules were passed through sieve number 16 and then lubricated with a mixture of HPMC K4 M, Magnesium stearate and talc. Then the lubricated granules were compressed into tablets using 20.3 X 9.8 mm, Capsule shaped flat punch on Cadmach single punch tablet machine.

2.5, Preparation of matrix tablets with HPMC K4 M.

Required quantities of Paracetamol & Avicel 101were weighed accurately and then they are blended uniformly. Required quantity of PVP K- 30 & 5 % Starch paste were taken and added to the above blend. The mixture was passed through sieve no. 10 to obtain the granules which were then mixed with the lubricants & HPMC K4 M and compressed into tablets using 20.3 x 9.8 mm capsule shaped flat punches on Cadmach single Punch tablet machine.

2.6, Preparation of Bilayer tablets containing Paracetamol and Tizanidine

Required quantities of Paracetamol & Avicel PH 101 were weighed accurately and blended uniformly. Then, the sufficient quantity of 5 % starch paste & PVP K-30 was added to above blend uniformly till to attain dough mass. The granules obtained were dried at 50^0C for 30min in RPD (Rapid process dryer) after passing through sieve number 10. The granules obtained were lubricated with HPMC K4M, Magnesium stearate, Sodium starch glycolate & Lactose (DCL 21) after passing through sieve

number 16. The immediate release layer containing Tizanidine, Pharmatose DCL 11 & Avicel 101 (Diluents) sieved in # 40, Colloidal silicon dioxide and Stearic acid (Lubricants) sieved in # 60 were taken in weighed quantities and mixed thoroughly for 10 minutes to attain uniform blend. Finally Lake of Quinoline yellow (colorant) sieved in # 100 was distributed in above blend by uniform mixing for another 10 minutes.

Weighed quantities of sustained release granules were subjected to slight compression after placing in the die cavity using Cad mach single punch tablet machine with 20.3 x 9.8 mm flat punches. Then immediate release granules in weighed quantities were filled and compressed with hardness of 250-255 Newton. Enough care was taken during weighing and filling the granules.

Formulae of Paracetamol SR Layer (Table no. 1)

Sl no	PCM (mg)	Guar gum (mg)	HPMC K100M (mg)	HPMC K4M (mg)	Starch (mg)	PVP K30 (mg)	Methyl Paraben (mg)	Propyl Paraben (mg)	Avicel 101 (mg)	SSG (mg)	Mag. stearate (mg)	Talc (mg)	Lactose DCL 11 (mg)
F 1	600	150	-	-	50	-	0.8	0.4	50	-	8	10	-
F 2	600	100	-	-	50	-	0.8	0.4	50	-	8	10	-
F 3	600	50	-	-	50	-	0.8	0.4	60	10	8	10	-
F 4	600	-	70	-	50	30	-	-	60	20	8	10	-
F 5	600	-	60	-	50	30	-	-	80	20	6	-	-
F 6	600	-	50	-	50	20	-	-	80	10	6	-	-
F 7	600	-	30	-	50	20	-	-	80	10	4	-	-
F 8	600	-	20	50	50	20	-	-	80	10	4	-	20
F 9	600	-	20	50	50	20	-	-	80	10	2	-	30
F 10	600	-	10	50	50	20	-	-	80	10	2	-	40
F 11	600	-	10	60	50	20	-	-	80	10	2	-	50
F 12	600	-	-	60	50	20	-	-	80	15	2	-	75
F 13	600	-	-	60	50	20	-	-	80	15	2	-	100
F 14	600	-	-	60	50	20	-	-	80	15	2	-	95

Formula of Immediate release layer containing Tizanidine (Table no. 2)

Sl no	Ingredients	Weights (mg)
1	Tizanidine Hcl	2.29
2	Pharmatose (DCL-11)	178.4
3	Avicel PH 112	45
4	Colloidal Silicon dioxide	2
5	Steric acid	2.2
6	Quinoline Yellow	1.009

3. EVALUATION

3.1, Evaluation of matrix formulations

3.1.1Weight variation

The weight variation test is carried out in order to ensure uniformity in the weight of the tablets in a batch. The total weight of 20 tablets from each formulation were determined and the average was calculated. The individual weights of the tablets were also determined accurately and the weight variation was calculated.

3.1.2, Hardness of tablets

The hardness of tablet is an indication of its strength. Measuring the force required to break the tablet across tests it. The force is measured in Newton and the hardness of about 5 kg/cm^2 is considered to

be satisfactory for uncoated tablets. Hardness of 10 tablets from each formulation was determined by Erweka hardness testers.

3.1.3, Friability test

Friability is the loss of weight of tablet in the container due to removal of fine particles from the surface. Friability test is carried out to access the ability of the tablet to withstand abrasion in packaging, handling and transport. Roche friabilator was employed for finding the friability of the tablets. 10 tablets from each formulation were weighed and placed in Roche friabilator that rotated at 25 rpm for 4 minutes. The tablets were dedusted and weighed again. The percentage of weight loss was calculated again. The percentage of weight loss was calculated using the formula % friability = [(W1-W2)100]/W1

Where, W1= Weight of tablet before test, W2 = Weight of tablet after test

3.1.4, Drug content uniformity

All the formulations were tested for their drug content. Ten tablets were taken and finely powdered. Powder equivalent to 25 mg of Paracetamol was accurately weighed and transferred into a 25ml volumetric flask and dissolved in small amount of 0.1 N HCL and then sonicated for 30 min and filtered. From this 1ml was taken and diluted to 10 ml to get 100 µg/ml stock solutions. From this 1ml and 2 ml were taken and diluted to 10 ml with 0.1 N HCl. The absorbances of these resulting solutions were measured at 280 nm and the drug content in the tablets was estimated from the standard graph. In case of bilayer tablets, the drug content of tizanidine can be determined by similar way at 230 nm using HPLC.

3.1.5, In vitro drug release studies

The Paracetamol matrix tablets and bilayer tablets were subjected to in vitro drug release studies in 0.1 N HCl for 8 hours to access the ability of the formulation for providing controlled drug delivery. Drug release studies were carried out in six stage dissolution test apparatus (Electrolab dissolution apparatus) using 900ml ml of dissolution medium (0.1 N HCl) maintained at 37±1^{0}C by using paddle type apparatus at 100 rpm.10ml of the sample from the dissolution medium were withdrawn at each time interval (1, 2, 4, 6 & 8 hours) and 10ml of fresh medium was replaced each time. The samples were filtered and from the filtrate 5ml were taken and diluted to 50ml with 0.1 N HCl. The absorbances of the sample were measured at λmax 280 nm using a UV spectrophotometer (For Paracetamol). For Tizanidine the drug release study is carried out by HPLC at 230 nm.

3.1.6, Kinetics of drug release

The cumulative amount of Paracetamol released from the formulations at different time intervals was fitted to zero order kinetics using least square method of analysis. The correlation coefficient between the time and cumulative amount released was calculated to find the fitness of the data to zero order kinetics. The data were also subjected to first order kinetics by determining the correlation coefficient between the time and the log percent of Paracetamol to be released from the formulation. The data were also subjected to Higuchi's model by plotting the cumulative percent Paracetamol released against square root of time. Fitness of Higuchi's model was assessed by determining the correlation coefficient between the square root of time and the cumulative amount of Paracetamol released from the formulations.

The data were also fitted to the model developed by Korsmeyer et al. In order to find out the drug release mechanism from the formulations. The cumulative percent of drug released from the formulations was plotted against time on log–log scale, and analyzed for linearity using Least-Squares Method. Calculating correlation coefficients between time and the cumulative percent of drug released on a log – log scale tested the fitness of the data.

3.2 STABILITY STUDIES

The stability studies of the optimized matrix formulations were done for about 3 months by packaging the tablets in a tightly closed bottle and kept in a humidity chamber. The physical characteristic like weight variation, hardness, friability, percent drug content and in vitro release profile were determined at an interval of 1st , 2nd ,3rd months.

Calibration Curve of Paracetamol in 0.1N HCl by UV (Table no. 3)

Concentration (mcg/ml)	Absorbance at 280 nm
0	0
10	0.1132
20	0.2198
30	0.3299
40	0.4580
50	0.5860
75	0.8206
100	1.1390

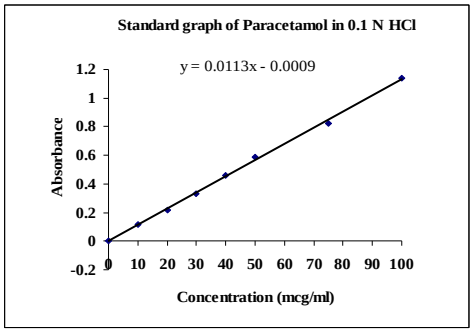

Figure 1

Calibration Curve of Paracetamol in 0.1N HCl by HPLC (Table no. 4)

0	0
1	230967
2	461908
3	692899
4	923696
5	1153783
6	1375923

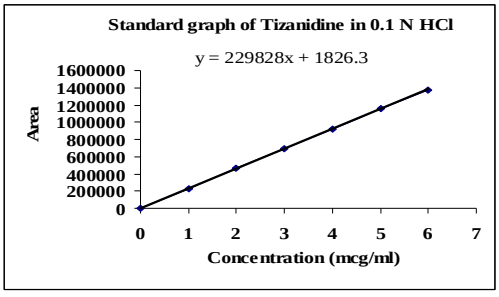

Figure 2

Preformulation data of Paracetamol & Tizanidine (Table no. 5)

Sl no	Preformulation data	Values for	
		Paracetamol	Tizanidine
01	Bulk density	0.6208 gm/cm^3	0.5944 gm/cm^3
02	Tapped density	0.7352 gm/cm^3	0.7442 gm/cm^3
03	Carr's index	15.56	20.12
04	Houseners ratio	1.184	1.252
05	Angle of repose	23.25	27.64

In-vitro dissolution kinetics of Paracetamol Matrix tablets (Table no. 6)

Formulations	Zero order	First order	Higuchi	n value
F1	0.9709	0.9828	0.9977	0.9998
F2	0.9796	0.9887	0.9938	0.9996
F3	0.9539	0.9623	0.9896	0.9940
F4	0.9881	0.9945	0.9867	0.9840
F5	0.9862	0.9949	0.9856	0.9792
F6	0.9870	0.9975	0.9891	0.9857
F7	0.9815	0.9968	0.9941	0.9947
F8	0.9408	0.9860	0.9814	0.9751
F9	0.9340	0.9836	0.9824	0.9811
F10	0.9250	0.9838	0.9827	0.9813
F11	0.9294	0.9931	0.9898	0.9848
F12	0.9423	0.9302	0.9952	0.9891
F13	0.9363	0.8929	0.9939	0.9808
F14	0.9613	0.7724	0.9984	0.9913

Invitro dissolution kinetics of Paracetamol & Tizanidine Bilayer tablets (Table no. 7)

Formulations	Zero order	First order	Higuchi	n value
FB1	0.9705	0.9417	0.9934	0.9950
FB2	0.9460	0.8701	0.9970	0.9940
FB3	0.9568	0.7943	0.9940	0.9919

Physical characteristics of Paracetamol tablets (Matrix layer) (Table no. 8)

Matrix formulations	% weight variation (n = 20)	Hardness ±SD Newton (n = 10)	Thickness (n = 10)	% Drug content (n = 10)	% Friability (n = 10)
F1	869.2 ± 4.286	151.7± 3.465	5.202± 0.031	97± 0.45	0.4347
F2	819.2± 4.191	154.4± 3.470	5.191± 0.030	97± 0.35	0.4227
F3	789.2± 4.149	152.6± 3.438	5.199± 0.037	99± 0.39	0.4155
F4	798.0± 4.253	154.3± 3.335	5.191± 0.036	100± 0.72	0.4155
F5	846.4± 4.072	154.6± 3.405	5.201± 0.039	98± 0.15	0.3956
F6	816.3± 4.130	153.2± 3.705	5.203± 0.038	99± 0.23	0.4351
F7	794.8± 4.060	154.2± 3.425	5.193± 0.032	98± 0.35	0.4261
F8	854.2± 4.145	152.3± 3.972	5.195± 0.037	98± 0.32	0.4291
F9	862.4± 4.194	151.4± 3.204	5.198± 0.029	99± 0.41	0.4322
F10	862.8± 4.110	153.7± 3.465	5.202± 0.032	98± 0.23	0.4362
F11	882.3± 4.158	151.9± 3.178	5.192± 0.032	98± 0.43	0.4319
F12	912.4± 3.835	153.5± 3.472	5.194± 0.036	99± 0.35	0.4289
F13	927.5± 3.971	158.0± 3.231	5.200± 0.037	99± 0.38	0.4348
F14	922.1± 3.935	155.4± 3.627	5.196± 0.039	99± 0.31	0.4352

Physical characteristics of Paracetamol & Tizanidine bilayer tablets (Table no.9)

Bilayer formulations	% weight variation (n = 20)	Hardness Newton (n = 10)	Thickness (n = 10)	% Drug content (n = 10)		% Friability (n = 10)
				Paracetamol	Tizanidine	
FB1	1150.4± 3.071	250.0± 3.231	5.212± 0.037	99.0± 0.45	98± 0.25	0.5347
FB2	1155.5± 1.663	254.4± 3.627	5.226± 0.039	98.9± 0.35	99± 0.35	0.5227
FB3	1152.5± 2.012	251.6± 3.225	5.221± 0.032	98.0± 0.39	99± 0.34	0.5155

Physicochemical characteristics of Paracetamol matrix tablets during stability study period (Table no. 10)

Formulation	Stability study Period	Weight variation (mg)	Hardness (Newton)	% Friability	% Drug content
F12	1st Month	912.4± 3.835	153.5± 3.472	0.4289	99.0± 0.35
	2nd Month	911.9± 3.583	153.1± 3.457	0.4289	98.8± 0.32
	3rd Month	911.87± 3.228	153.1 ± 3.467	0.4289	98.9± 0.30
F13	1st Month	927.50± 3.971	158.0± 3.231	0.4348	99.0± 0.31
	2nd Month	927.01± 3.964	157.9± 3.212	0.4289	98.7± 0.29
	3rd Month	926.94± 3.956	157.89± 3.204	0.4289	99.0± 0.30
F14	1st Month	922.10± 3.935	155.4± 3.627	0.4352	99.0± 0.38
	2nd Month	921.97± 3.913	155.1± 3.614	0.4352	98.6± 0.35
	3rd Month	921.82± 3.897	154.9± 3.601	0.4352	98.7± 0.29

Physicochemical characteristics of Paracetamol & Tizanidine bilayer tablets during stability study (Table no.11)

Formulations	Stability study Period	Weight variation (mg)	Hardness (Newton)	Friability	% Drug content of Paracetamol	Tizanidine
FB1	1st Month	1150.9± 1.071	251.6± 3.231	0.5155	99.1± 0.45	98.0± 0.45
	2nd Month	1150.6± 1.063	251.4± 3.627	0.5152	98.8± 0.35	97.9± 0.34
	3rd Month	1150.1± 1.012	251.6 ± 3.225	0.5155	98.9± 0.39	97.7± 0.38
FB2	1st Month	1155.9± 2.031	251.8± 3.214	0.5551	99.0± 0.51	99.0± 0.15
	2nd Month	1155.6± 2.025	255.6± 3.206	0.5550	98.5± 0.23	98.9± 0.23
	3rd Month	1155.1± 2.016	255.6± 2.998	0.5549	99.0± 0.35	99.01± 0.35
FB3	1st Month	1152.5± 2.012	255.3± 3.109	0.5972	99.0± 0.41	99.0± 0.41
	2nd Month	1152.1± 2.002	253.3± 2.994	0.5962	98.5± 0.34	98.7± 0.34
	3rd Month	1152.0± 1.997	253.4± 3.012	0.5963	98.6± 0.45	98.9± 0.45

Zero order release profile of F1, F2& F3 (Guar gum) Matrix tablets.
Table No 12

Time in Hrs	Cumulative % drug dissolved		
	F1	F2	F3
0	0	0	0
1	7.7	8.4	10.5
2	12.5	13.4	17.2
4	19.7	21.7	24.4
6	25.5	28.5	30.2
8	31.3	35.9	38.6

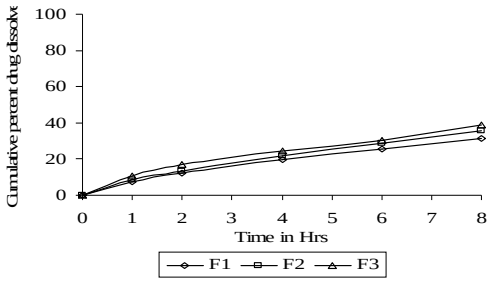

Figure 3

Zero order release profile of F4, F5, F6 & F7 (HPMC K100 M) Matrix tablets
Table No 13

Time in Hrs	Cumulative % drug dissolved			
	F4	F5	F6	F7
0	0	0	0	0
1	6.2	7.15	8.71	10.61
2	10.2	11.20	13.58	17.21
4	26.8	29.80	31.76	34.72
6	37.6	39.45	41.79	43.84
8	45.4	48.8	51.54	54.21

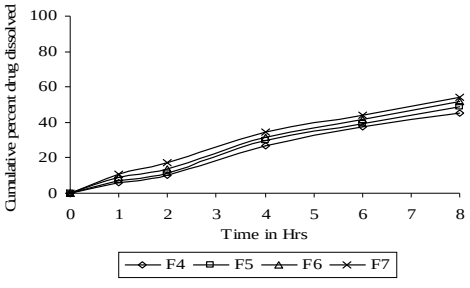

Figure 4

Zero order release profile of F8, F9, F10 & F11 (HPMC K100 M & HPMC K4 M)
Matrix tablets
Table no 14

Time in Hrs	Cumulative % drug dissolved			
	F8	F9	F10	F11
0	0	0	0	0
1	13.71	16.73	18.42	21.39
2	26.6	29.42	33.32	36.65
4	49.82	52.76	55.43	58.92
6	58.23	61.27	64.29	67.91
8	66.24	69.46	72.63	79.42

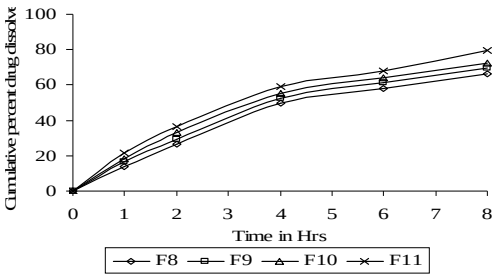

Figure 5

Zero order release profile of F12, F13, F14 (HPMC K4 M)
Matrix tablets
Table no 15

Time in Hrs	Cumulative % drug dissolved		
	F12	F13	F14
0	0	0	0
1	22.5	26.47	22.41
2	41.6	48.39	42.02
4	68.01	67.09	66.31
6	82.41	85.41	86.62
8	94.20	98.60	99.90

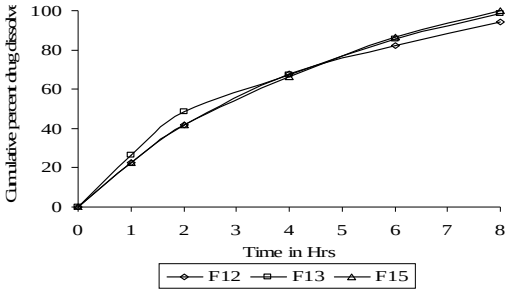

Figure 6

Zero order release profile of FB1, FB2 & FB3.
Table No 16

Time in Hrs	Cumulative % drug dissolved		
	FB1	FB2	FB3
0	0	0	0
1	22.2	25.9	23.02
2	34.9	43.8	40.32
4	63.3	69.8	69.21
6	85.6	87.2	88.83
8	97.9	99.32	99.90

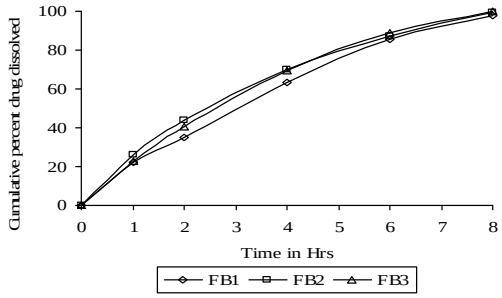

Figure 7

4. RESULTS AND DISCUSSION

In the present piece of investigation Matrix tablets of Paracetamol & Bilayer tablets of Paracetamol & Tizanidine were prepared successfully with hydrophilic polymers like Guar gum, HPMC K100 M and HPMC K4 M by wet granulation technique. Solubility studies of Paracetamol & Tizanidine were performed. The solubility of selected drugs was found to be maximum in 0.1N HCl and minimum in water. The results of Preformulation studies are depicted in table no 05. The results revealed that all experimental powders exhibited good flow characteristics. The results of Physical characteristics of matrix layer tablets and bilayer tablets are presented in table no. 08 & 09. The results of weight variation lie in the range of 789.2 mg to 927.5 mg for matrix layer tablets & 1150.4mg to 1155.5mg for bilayer tablets indicating that the variation in the weight of the tablets is within official limits. The hardness test was carried out using erweka hardness

tester. The hardness of the tablets was found to be uniform and in the range of 151.4 to 158.0 Newtons for matrix layer tablets & 250.0 to 254.4 Newtons for bilayer tablets, indicates that the prepared tablets are mechanically stable. The friability test was carried out by Roche Friabilator. The percentage friability of matrix layer tablets are in the range of 0.39% to 0.43% and Bilayer tablets in the range of 0.51% to 0.53%, which is less than the standard limit of 1% indicating that the prepared tablets are mechanically stable. The results of percent drug content for Paracetamol is in the range of 97% to 100% for matrix layer tablets & 98% to 99% for bilayer tablets, respectively and the percent drug content for Tizanidine in Bilayer tablets is in the range of 98 to 99%, which is within the standard limit of ± 5%. It indicates uniform distribution of drugs in the tablets of each formulation. The Paracetamol matrix tablets and Paracetamol & Tizanidine Bilayer tablets were subjected to in vitro drug release studies in pH 0.1 N Hcl for 8 hours to assess the ability of the formulation for providing controlled drug delivery. Drug release studies were carried out in eight stage Type 2 dissolution test apparatus (Electrolab) using 900ml ml of dissolution medium, maintained at 37±1^{0}C at 100 rpm.

4.1, Matrix tablets

The drug release profiles of Paracetamol matrix tablets were subjected to study the kinetic behavior using various mathematical models like Zero order, First Order, Higuchi, Korsemayer release kinetics. The correlation coefficient values of zero order release profiles of Guar gum matrix tablets (F1, F2, and F3) are 0.9709, 0.9796 & 0.9539. The first order release profiles of Guar gum matrix tablets are 0.9828, 0.9887& 0.9623.The release kinetic data indicates that drug release from the formulation follows First order kinetics. The correlation coefficient values of Zero order release profiles of HPMC K100M matrix tablets (F4, F5, F6 and F7) are 0.9881, 0.9862, 0.9870 & 0.9815.The First order release profiles of HPMC K100M matrix tablets are 0.9945, 0.9949, 0.9975& 0.9968. The release kinetic data indicate that drug release from the formulation followed First order kinetics. The correlation coefficient values of zero order release profiles of HPMC K100 M & HPMC K4 M matrix tablets (F8, F9, F10 and F11) are 0.9408, 0.9340, 0.9250, & 0.9294 and first order release profiles of HPMC K100 M & HPMC K4 matrix tablets are 0.9860, 0.9836, 0.9838 & 0.9931.The correlation coefficient values indicate that drug release from the formulations follows First-order kinetics. The correlation coefficient values of zero order release profiles of HPMC K4 M matrix tablets (F12, F13 and F14) are 0.9423, 0.9363, & 0.9613 and first order release profiles of HPMC K4 M matrix tablets are 0.9302, 0.8929 & 0.7724. The correlation coefficient values indicate that drug release from the formulations follows Zero order kinetics. The correlation coefficient values of Higuchi plot are 0.9977, 0.9938 & 0.9896 for Guar gum matrix tablets (F1, F2, and F3), 0.9867, 0.9856, 0.9891& 0.9941 for HPMC K100M matrix tablets (F4, F5, F6 and F7), 0.9814, 0.9824, 0.9827 & 0.9898 for HPMC K100 M & HPMC K4 M matrix tablets (F8, F9, F10 and F11) and 0.9952, 0.9939 & 0.99849941 for HPMC K4 M matrix tablets. The correlation coefficient values are close to one which indicates that the drug release is by diffusion mechanism. When the percent of drug released from formulations F1, F2, & F3 were fitted to the model developed by Korsmeyer et al. the mean diffusional exponent values (n) ranged from 0.9940 to 0.9998 indicating that Paracetamol release from Guar gum matrix tablets followed anomalous diffusion. The diffusional exponent values (n) for F4, F5, F6 and F7 ranged from 0.9792 to 0.9947 indicating that the drug release from the HPMC K100 MCR matrix tablets followed anomalous diffusion. The diffusional exponent values (n) for F8, F9, F10 & F11 ranged from 0.9751 to 0.9848 indicating that the drug release from the HPMC K100 M & HPMC K4 M matrix tablets followed anomalous diffusion. The diffusional exponent values (n) for F12, F13 & F14 ranged from 0.9808 to 0.9913 indicating that the drug release from the HPMC K4 M matrix tablets followed anomalous diffusion.

4.2, Bilayer tablets

The correlation coefficient values of zero order and first order release profiles of HPMC K4M bilayer tablets (FB1, FB2 and FB3) are 0.9705, 0.9460 & 0.9568 and 0.9417, 0.8701 & 0.7943 respectively. The correlation coefficient value indicates that drug release from the formulation followed zero order kinetics. The correlation coefficient values of Higuchi plot are 0.9934, 0.9970 & 0.9940 for HPMC K4M bilayer tablets. The correlation coefficient values are close to one which indicates that the drug release is by diffusion mechanism. The diffusional exponent values (n) for FB1, FB2 & FB3 ranged from 0.9919 to 0.9950 indicating that the drug release from the HPMC K4M matrix tablets followed anomalous diffusion. In both the matrix and bilayer tablets the dissolution rate decreases with an increase in the concentration of the polymer.

5.3, Selection of optimized formulation of Paracetamol Matrix tablets & (Paracetamol & Tizanidine) Bilayer tablets.

4.3.1, Matrix tablets

The dissolution profile of Paracetamol Matrix tablets was carried out. From the dissolution data it concludes that, the tablets prepared from Guar gum, HPMC K100 M, polymers posses a very low drug release profile. Whereas the tablets prepared from HPMC K4 M polymer (F12, F13 & F14) posses a drug release of more than 95%.Thus, the above mentioned formulations are chosen as optimized formulation and used for preparation of bilayer tablets.

4.3.2, Bilayer tablets

The dissolution profiles of Paracetamol & Tizanidine Bilayer tablets were carried out. In case of Bilayer tablets from all the formulations, the drug was released at a rate of 22-25% in 1st hour & shows more than 97% release in 8th hour. From the immediate release layer, the drug was completely released within 15 minutes. The Bilayer tablets, prepared from HPMC K4 M showed same release profile as that of F12, F13 & F14 matrix formulations. So, the Bilayer tablets corresponding to the Matrix tablets F12, F13 and F14 that are FB1, FB2 and FB3 are considered to be the optimized formulations.

4.4., Drug-excipients interaction studies

The optimized formulations were subjected to FTIR studies to confirm whether or not there is drug polymer interaction. The results of the FTIR studies indicate that there was no interaction between the drug and polymers used in the formulation.

5.5, Stability studies

The stability studies were subjected to optimized matrix formulations as well as Bilayer formulations for the period of three months in air tighten and closed containers. The stability studies were performed in humidity chamber maintaining at 40 °C and 75%RH. The physical characteristic like weight variation, hardness, friability, percent drug content and in vitro release profile were determined at 1st,2nd & 3rd month. The results of weight variation, hardness, friability and percent drug content during stability studies for Matrix & Bilayer tablets are shown in the table no. 10 & 11 respectively. These values indicate that there were no appreciable changes when compared with original samples. Dissolution study was carried out at regular time interval for all the optimized formulation during the stability studies. The cumulative percentage drug released for Matrix & bilayer tablets were studied. The results indicate that, no appreciable changes were observed in the release profile of the formulations during the stability studies. The data obtained from the stability studies of the optimized formulations indicates that the tablets are physically stable.

CONCLUSIONS

A study involving preparation and evaluation of matrix as well as bilayer tablets were made. Physicochemical parameters of matrix & bilayer tablets were performed. *In vitro* drug release profiles of matrix & bilayer tablets were performed. The matrix formulations (F12, F13 & F14) containing HPMC K4 M (60mg), SSG (15mg) & Lactose (DCL 21) 75,95,103 mg respectively, Exhibited good release profile as compared to the other formulations. Hence, these formulations are considered to be optimized formulations. Based on in vitro drug release profile, it was found that the release of medicaments from prepared matrix tablets (F12, F13 & F14) follows zero order and the release of medicaments from prepared bilayer tablets (FB1, FB2 & FB3) also follows Zero order. The IR studies confirmed that, no drug – polymer interactions exist in Matrix formulations (F12, F13 & F14) as well as in Bilayer formulations (FB1, FB2 & FB3). In conclusion, the Bilayer tablets of Tizanidine & Paracetamol could be formulated using HPMC K4 M polymer, which is much more effective in treating Rheumatoid arthritis, Osteoarthritis & other severe pain syndromes. However, long term stability studies are needed to establish stable tablet formulations. Further clinical trials are needed to establish its efficacy in treatment of Arthritic pain.

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