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FORMULATION AND IN-VITRO EVALUATION OF TRIFLUOPERAZINE HYDROCHLORIDE BILAYER FLOATING TABLET

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ABSTRACT

The purpose of this study is to prepare a bilayer gastro retentive tablet of Trifluoperazine hydrochloride using direct compression technology and optimize the type and concentration of polymer to give maximum retentive effect with good drug release profile. Trifluoperazine hydrochloride having biological half life (7-8 hr) was selected model drug as it is neuroleptic, antiemetic agent used to treat schizophrenia, anxiety disorder & other psychoses having first pass metabolism, low oral bioavailability, maximum absorption in the upper part of GIT hence it is suitable for gastro retentive system. In this study, a bilayer tablet was prepared which contains an immediate release portion and a floating layer.Immediate release of drug controlled by superdisintegrant sodium starch glycolate. starch microcrystalline cellulose were used as diluents. For Sustain Release Layer various hydrophilic & hydrophobic polymers such as HPMC K100M, CP934 &EUDRAGIT RS100 were used. Sodium bicarbonate, and citric acid as gas generating agent, DCP as additive combine with the polymer to form the floating layer .The optimum concentration of sodium bicarbonate was found to be 14% for floating buoyancy. The bilayer tablets were characterized by lag time, floating time, weight variation, drug content and dissolution profile. It is concluded on the basis of buoyancy and in-vitro release kinetics that optimized formulation FL-7 containing diluents to total polymer ratio 1:3 &HPMC K100M to CP 934ratio 3:0.5 gave the best in-vitro release of 97.33% in 12 hrs was carried out in 1.2 pH.

KEYWORDS: *Trifluoperazine hydrochloride, bilayer floating drug delivery system, sustained release, CP934 &EUDRAGIT RS100*

INTRODUCTION

Development of oral controlled release systems has been a challenge to formulation scientists because of the difficulty in localizing the system in target areas of the gastrointestinal tract. In recent years, per oral dosage forms for gastric retention have attracted more and more attention for their theoretical advantage in gaining control over the time and the site of drug release. This would be particularly valuable for drugs that exhibit an absorption window in the upper part of the small intestine. Gastric retention has received significant interest in the past few decades as most of the conventional oral delivery systems have shown some limitations related to fast gastric emptying time. A gastro retentive dosage form (GRDF) can overcome this problem and is particularly useful for drugs that are primarily absorbed in the duodenum and upper jejunum segments. Food effects and the complex motility of the stomach play a major role in gastric retention behaviour. Several approaches of non-effervescent and effervescent formulation technologies have been used and patented in order to increase gastric residence time of the GRDF.[1]

The aimed delivered system provides the prolonged release of a single dose, thereby minimizing the frequent administration and hence total dose required to elicit pharmacological activity, thereby reducing the side effects. Particularly bilayer tablets are commonly used to avoid chemical incompatibilities of formulation components by physical separation, and release profiles may be modified by combining layers with different release patterns, or by combining slow release with immediate release layers.[2] In present study bilayer tablets of Trifluoperazine hydrochloride were prepared. Trifluoperazine hydrochloride is widely used in the treatment of psychotic conditions, acute and chronic

schizophrenia, manic phase of manic depressive disorder, anxiety disorder and agitation either alone or in combination with other antipsychotic agents. Trifluoperazine hydrochloride has low oral bioavailability due to considerable first-pass metabolism therefore, to maintain the systemic drug concentration consistently above its target therapeutic concentration, thus necessitating frequent administration of large doses to maintain therapeutic drug level. The side effects of Trifluoperazine hydrochloride are dose dependent and a reduction of the total administered dose reduces the severity of the toxicity, thus the frequent dosing of large doses due to low oral bioavailability makes the Trifluoperazine hydrochloride, a good candidate for gastroretentive drug delivery system.[3]

This may be in terms of a reduction in the number of doses to be taken to achieve the desired therapeutic effect, therefore reducing overall medication cost, or the subsequent improvement in compliance. Several approaches are currently used to prolong gastric retention time. These include floating drug delivery systems, also known as hydrodynamically balanced systems, swelling and expanding systems, polymeric bioadhesive systems, modified-shape systems, high-density systems, and other delayed gastric emptying devices. [4,5,6]

MATERIALS AND METHODS :

Trifluoperazine hydrochloride Haffkin Ajanta Private Limited, Jalgaon. HPMC K100M Ethypharm LL Private Limited, Mumbai. Carbopol 934P Vishal Chem, Mumbai, Eudragit RS100 Evonik Industries, Germany Microcrystalline cellulose Loba chemical, Mumbai Maize Starch Loba chemical, Mumbai.

Preparation of bilayer tablet :

All ingredients of each layer were weighed properly and passed through sieve No. 60. The ingredients of immediate layer and sustain layer were mixed separately in mortar and the ingredients of immediate layer lubricated with magnesium stearate (1 % w/w) and aerosil (1 % w/w). The composition of immediate release layer is kept constant for all formulations. Powder mixture of sustain layer was transferred manually into the die cavity, Slightly compressed sustain release powder and then powder mixture of immediate layer was transferred over the sustain layer, finally after addition of the immediate layer into the die cavity, the total die cavity content was compressed with 9 mm diameter concave punch tooling. Each bilayer tablet contained 6 mg (2 mg as immediate release dose and 4 mg as sustained dose) of Trifluoperazine hydrochloride. Compression was controlled to produce a 5 kg/cm^2 tablet crushing strength.[7]

Table No.1:- Composition of immediate release layer (IRL) of bilayer floating tablet.

Composition	Quantity (mg)
Trifluoperazine hydrochloride	2
Maize starch	4.5
Sodium starch glycolate	7.5
Magnesium stearate	0.75
Aerosil	0.75
Microcrystalline cellulose	59.5
Ferric oxide yellow	q. s.

Table No.2:- Floating layer (FL) design.

Diluent : Total Polymer Ratio	HPMC K100M : Other Polymers Ratio
3 : 1	3 : 0.5
2.5 : 1.5	2.5 : 1
2 : 2	2 : 1.5
1.5 : 2.5	1.5 : 2
1 : 3	
0.5 : 3.5	

Table No.3:- Composition of floating layer (in mg) for formulation FL-1 TO FL-14

Ingredients	FL1	FL2	FL3	FL4	FL5	FL6	FL7	FL8	FL9	FL10	FL11	FL12	FL13	FL14
Trifluoperazine hydrochloride	4	4	4	4	4	4	4	4	4	4	4	4	4	4
***HPMC K100M**	30	45	60	75	90	105	77.13	64.27	51.42	38.56	77.13	64.27	51.42	38.56
Carbopol 934P	-	-	-	-	-	-	12.85	25.71	38.56	51.42	-	-	-	-
Eudragit RS100	-	-	-	-	-	-	-	-	-	-	12.85	25.71	38.56	51.42
#DCP	90	75	60	45	30	15	30	30	30	30	30	30	30	30

EVALUATION PARAMETERS FOR PREPARED FORMULATIONS:

Evaluation of Powder Mixture:-

The flow properties of granules were evaluated in terms of angle of repose, Carr index and Hausner's ratio. The angle of repose of immediate release and sustain release layer was determined by fixed funnel method. For determination of angle of repose (θ) the granules were poured through the walls of a funnel, which was set at a place such that its lower tip was at a height of closely 2.0 cm above from ground surface. The granules were poured up to the time when upper tip of the pile surface touched the lower tip of the funnel. The tan¯1 of (height of the pile / radius of its base) give the angle of repose. Granules were poured gently through a glass funnel into a graduated cylinder cut exactly to 10 ml mark. Excess granules were removed using a spatula and the weight of the cylinder with pellets required for filling the cylinder volume was calculated. The cylinder was then tapped from a height of 2.0cm until the time when there was no more decrease in the volume. Bulk density (ρb) and tapped density (ρt) were calculated. Carr index (IC) were calculated according to the two equations which are follows:- [8,9]

$$IC = \rho t - \rho b / \rho t$$

Evaluation of bilayer floating tablets:-

1. Thickness:-

The thickness of the tablets was determined using a micrometer screw gauge. Three tablets from each type of formulation were used and average values were calculated. [10]

2. Hardness:-

Tablet hardness has been defined as the force required breaking a tablet in a diametric compression test. A tablet was placed between two anvils of hardness tester, force was applied to the anvils, and the crushing strength that causes the tablet to break was recorded in kg/cm^2.[10]

3. Weight variation:-

The weight variation test is done by taking 20 tablets randomly and they were weighed accurately. The composite weight divided by 20, provides an average weight of tablet. Not more than two of the individual weight deviates from the average weight by 5 %. And none should deviate by more than twice that percentage. The average weight and standard deviation of the tablets were calculated.[11]

4. Friability:-

Tablets require certain amount of strength or hardness and resistance to withstand mechanical shock of handling in manufacturing, packaging, and shipping. A pre-weighed sample (10 tablets) were placed in the friabilator, and operated for 100 revolutions, then again weighed the tablets. Percentage loss should not more than 0.5 to 1.0 % and the % friability was calculated using the formula.[10,11]

Where,

$$\% \text{ Friability} = \frac{W_0 - W}{W_0} \times 100$$

W_0 -Weight of tablet before test,
W - Weight of tablet after test.

5. Uniformity of content:- One tablet was transferred to a 100 ml volumetric flask; to it 50 ml of 0.1 N HCl was added and heated on steam bath for 50 minutes. The heated solution was sonicated for about 10 min. The solution was allowed to cool, diluted with 0.1 N HCl to volume, mixed and finally filtered. The accurately measured amount (1 ml) of the filtrate was diluted up to 10 ml with 0.1 N HCl to obtain a test preparation containing about 6 µg/ml of Trifluoperazine hydrochloride. Concomitantly the absorbance of test and standard preparation was determined at 255 nm. The same procedure was repeated for nine tablets. [11]

6. Floating behavior:-

Floating behavior studies were performed on the floating tablet. The study was carried out in a USP Dissolution Test Apparatus (Type II) at paddle speed 75 rpm in 900 ml of 0.1 N HCl at 37 ± 0.5° C to mimic *in-vivo* conditions. The time interval between the introduction of the tablet into the dissolution medium and its buoyancy to the top of dissolution medium was taken as floating lag time. Also the duration of system floatation and the relative matrix integrity was observed visually. [12]

7. *In-vitro* dissolution study:-

The release rate of Trifluoperazine hydrochloride from bilayer floating tablets was determined using USP Dissolution Test Apparatus (Type II). The dissolution test was performed using 900 ml of 0.1 N HCl, at 37 ± 0.5°C with the paddle speed of 75 rpm. (Rao MRP, *et al.* 2009). Aliquot (10 ml) of the solution was collected from the dissolution apparatus at interval of 30 min and then hourly upto 12 hrs and were replaced with fresh dissolution medium. Absorbances of these solutions were measured at 255 nm. Aliquots were withdrawn from a zone midway between the surface of dissolution medium and the top of rotating paddle not less than 1 cm apart from the vessel wall. Cumulative percentage drug release was calculated by using an equation obtained from a standard curve. [13]

8. Swelling characteristics:-

To evaluate the water penetration characteristics, the pre-weighted tablets were immersed in 500 ml beaker containing simulated gastric fluid (SGF) and maintained for 12 hrs at 37 ± 0.5^{0}C. Swollen tablets were removed from the solution, immediately wiped with a paper towel to remove surface droplets, and weighed. The % swelling index (Sw) was calculated according the following equation;

$$\% \text{ Swelling index (Sw)} = \frac{W_t - W_0}{W_0} \times 100$$

Where,

W_0 - Initial weight of tablet,

W_t - Weight of the swollen tablet at time t. [14]

RESULT AND DISCUSSION

Floating lag time , Floating time :

Table No.4:- Floating ability of various bilayer tablet formulations.

Formulation code	Floating lag time (Sec)	Floating time (Hrs.) ± SD
FL-1	not float	not float
FL-2	not float	not float
FL-3	not float	not float
FL-4	79.6 ± 1.52	9.16 ± 0.06
FL-5	102.0 ± 1.00	10.31 ± 0.14
FL-6	157.6 ± 2.51	18.23 ± 0.23
FL-7	101.3 ± 3.51	15.33 ± 0.14
FL-8	144.0 ± 3.00	18.29 ± 0.26
FL-9	175.6 ± 2.51	21.37 ± 0.07
FL-10	278.6 ± 3.05	4.40 ± 0.72
FL-11	108.0 ± 3.60	16.28 ± 0.10
FL-12	162.3 ± 4.04	19.37 ± 0.10
FL-13	203.0 ± 4.00	22.14 ± 0.07
FL-14	457.6 ± 3.51	8.22 ± 0.15

Table No.5:- Evaluation parameters of all formulations.

Formulations	Angle of Repose (θ)	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Carr's Index (%)	Thickness (mm) ±SD (n=3)	Weight Variation (mg) ±SD (n=20)	Hardness (kg/cm^2)±SD (n=3)	Friability (%)±SD (n=3)	Uniformity of Content(%) ±SD (n=10)
IL	30.29±0.95	0.65 ±0.75	0.73 ±0.59	10.72 ±0.78	-	-	-	-	-
FL-4	29.22±0.46	0.95 ±0.58	1.05 ±0.42	9.29 ±0.47	3.83 ±0.14	254.8±0.60	4.4±0.47	0.71 ±0.09	98.39 ±0.73
FL-5	27.84 ±0.92	0.74 ±0.81	0.78 ±0.61	5.56 ±0.75	3.78 ±0.13	254.7±0.53	4.8±0.50	0.52 ±0.12	98.65 ±0.75
FL-6	32.44 ±0.46	0.67 ±0.49	0.84 ±0.51	20.39 ±0.76	3.68 ±0.11	255.0±0.51	4.6±0.65	0.56 ±0.20	98.96 ±0.99
FL-7	30.44 ±0.95	0.68 ±0.62	0.76 ±0.69	10.91 ±0.63	3.74 ±0.19	255.0±0.50	4.5±0.72	0.65 ±0.08	99.15 ±0.49
FL-8	31.98 ±0.92	0.74 ±0.47	0.88 ±0.71	16.15 ±0.57	3.75 ±0.12	254.9±0.63	4.9±0.61	0.64 ±0.09	98.96 ±0.68
FL-9	32.44 ±0.84	0.62 ±0.39	0.77 ±0.63	18.91 ±0.56	3.84 ±0.11	254.8±0.57	4.4±0.46	0.57 ±0.31	99.57 ±0.30
FL-11	30.14 ±0.46	0.64 ±0.45	0.72 ±0.49	10.18 ±0.87	3.81 ±0.14	255.1±0.51	5.0±0.55	0.71 ±0.18	98.49 ±0.60
FL-12	31.21 ±0.85	0.53 ±0.61	0.62 ±0.47	14.43 ±0.81	3.70 ±0.12	254.7±0.70	4.6±0.45	0.55 ±0.07	98.18 ±0.79
FL-13	33.36 ±0.92	0.47 ±0.72	0.61 ±0.54	21.67 ±0.74	3.74 ±0.11	254.5±0.77	4.5±0.29	0.57 ±0.24	98.79 ±0.82

The formulation batch containing HPMC K100M and Eudragit RS100 showed higher swelling index than the formulation containing HPMC K100M, HPMCK100M and Carbopol 934P, while formulation containing HPMC K100M showed lower swelling index. The % swelling index of all formulation is shown in fig.. From the results obtained, it was observed that the increased concentration of Carbopol 934P and HPMC K100M in the formulations increases the swelling indices.

Figure No.1: % swelling index of formulations from FL-4 to FL-9 and FL-11 to FL-13.

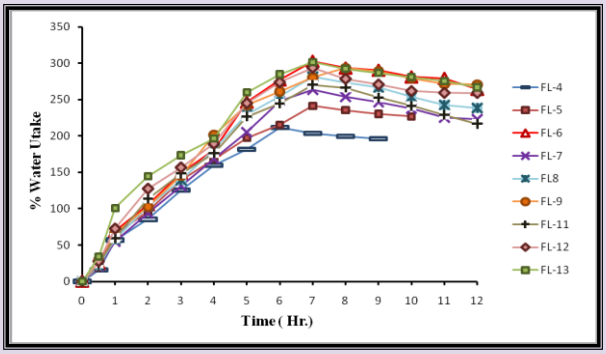
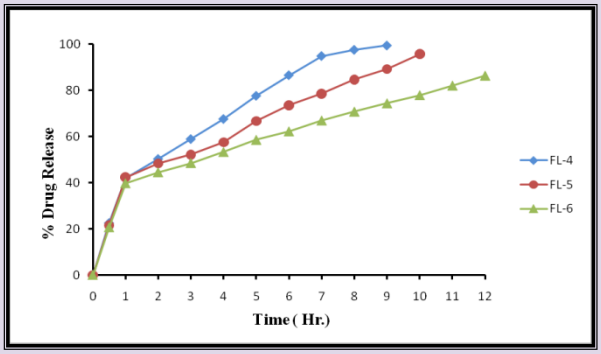


Figure 2:- *In-vitro* release profile of formulations from FL-4 to FL-6



The formulation FL-4, FL-5, FL-6 prepared with different diluent to total polymer ratio by taking HPMC K100M as single polymer showed tablet floating time in the range of 9, 10 to 18 hrs respectively, the percent drug release was observed between 99.29 %, 95.61 % and 86.29 % respectively.

Figure No.3:- *In-vitro* release profile of formulations from FL-7 to FL-9

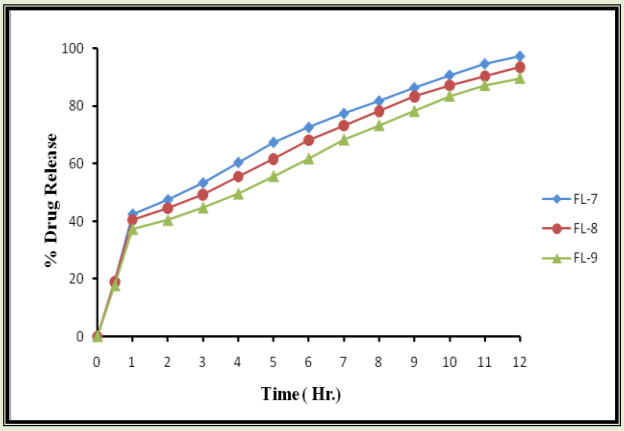
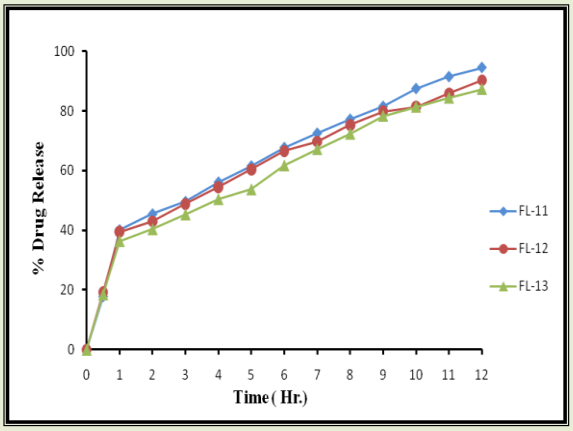


Figure No.4:- *In-vitro* release profile of formulations FL-11 to FL-13



The formulations FL-7, FL-8, FL-9 prepared with HPMC K100M and Carbopol 934P float for more than 12 hrs and percent drug release was observed between to 97.33 %, 93.49 % and 89.73 % respectively. The formulation FL-7 showed higher drug release than other formulations.

The formulations FL11, FL12, FL13 prepared with HPMC K100M and Eudragit RS100 float for more than 12 hrs and percent drug release was observed between 97.33 %, 93.49 % and 89.73 % respectively at the end of 12 hrs.

CONCLUSION

Initially for biphasic release of drug, immediate release layer of bilayer tablet containing Trifluoperazine hydrochloride was prepared by using superdisintegrant i.e., sodium starch glycolate, starch and microcrystalline cellulose as a diluents. Sustaine release layer was prepared by using various hydrophilic and hydrophobic polymers such as HPMC K100M, CP 934 and Eudragit RS100.Bilayer tablets when comes in contact with gastric fluid quickly releases the immediate release layer and start onset of action, subsequently floating sustained release layer floats over gastric fluid and release the drug in sustained manner. It was concluded on the basis of buoyancy and *in-vitro* release kinetics that optimized formulation FL-7 containing diluents to total polymer ratio 1:3 and HPMC K100M to CP 934 ratio 3:0.5 gave the best *in-vitro* release of 97.33% in 12 hrs was carried out in 1.2 pH (simulated gastric fluid), bilayer floating tablet showed sustained release of the drug in acidic condition (pH 1.2) and the drug release was found to be approximately linear. Approximately 40 % of the drug was released initially in first hour. The optimized dosage form can control the release, avoid dose dumping and extend the duration of action of a drug with prolong floating time.

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