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FORMULATION AND EVALUATION OF VERAPAMIL HYDROCHLORIDE FLOATING MATRIX TABLETS

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ABSTRACT

The present study was aimed to preparing a floating drug delivery system to design a controlled release oral dosage form of Verapamil Hydrochloride to overcome the demerit of the limited residence time of the controlled release dosage form in the gastrointestinal track and hence to increase the duration of release, The intragastric hydro dynamically balanced or floating system was convenient, Hence hydrophilic polymer was choosed as the matrix material, which swell and float in the medium. This swelling retardant was used to control the release of drug. To formulate and prepare the single layered intragastric floating delivery system of verapamil hydrochloride by direct compression method with hydroxyl propyl methyl cellulose (HPMC k4m and k15m) each alone or in combination with different drug: polymer ratios. Thus the study aims to improve the oral bioavailability of the drug and to achieve extended retention in the stomach which may result in prolonged absorption. Tablets were evaluated by different parameters such as weight uniformity, thickness, hardness test, friability test, swelling index, Buoyancy studies and In vitro release studies. Conclusion of this study was the % drug release was found to be 95.13 %, The Marketed product gave 92.25 % of drug release in 8 hours of dissolution study. The formulation F1 with 95.13 % of drug release has better control over release of drug was compared with marketed product.

Keywords: Verapamil Hydrochloride, Hydroxy Propyl Methyl Cellulose K4m and K15m, Direct compression method, Floating Matrix Tablet, Evaluation and Invitro Studies.

INTRODUCTION

Tablets may be defined as solid pharmaceutical dosage forms containing drug substances with or without suitable diluents and prepared either by compression or molding methods. They have been in wide spread use since the later part of the 19th century and their popularity continues. The term compressed tablet was believed to have been first used by "JOHN WYETH". During the same period, molded tablets were introduced to be used as Hypodermic tablets for injections (Donald *et al*., 2005).

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Most of the orally administered dosage forms have several physiological limitations, such as GI transit time, incomplete drug absorption due to incomplete release of drug from the devices and too short residence time of the dosage forms in the absorption region of GI tract. To overcome these limitations, many attempts have been made by scientists by designing various drug delivery systems. Among these systems, Floating drug delivery systems (FDDS) is one of the approaches which remain buoyant due to their lower density that of the GI and intestinal fluids. Both single and multiple unit systems have been developed (Donald *et al*., 2005 and S. P. Vyas *et al*., 2007).

The matrix tablets may be manufactured by direct compression of the blend of active ingredient,

retardant material and additives. The hydrophilic matrix requires water to activate the release mechanism and several advantages including ease of manufacture, release of 100% drug in in-vivo and excellent uniformity of matrix tablets. The hydrophilic matrix tablets are immersion in water quickly forms a gel layer around the tablets. Drug release is controlled by gel diffusion barrier. The matrix building materials with fast polymer hydration capability is the best choice to be use in hydrophilic matrix formulation (Siahi *et al*., 2005).

Verapamil hydrochloride belongs to a class called calcium channel blockers. These medications block the movement of calcium into the muscle cells of the coronary arteries. Calcium triggers contraction of muscles, blocking entry of calcium relaxes the arterial muscles. This relaxation allows the arteries to become larger so that more blood can flow through them. Verapamil hydrochloride is useful in treating and preventing chest pain (Angina) resulting from spasm (contraction) of the coronary arteries that reduces the flow of blood to the heart (Goodman and Gilmans, 2010).

MATERIALS AND METHODS

MATERIALS

Verapamil Hydrochloride was obtained as a gift sample from Alpex International Pvt Ltd, Kolkata. Hydroxyl propyl methyl cellulose (K4M and K15M) was obtained as a gift sample from Loba Chemie Pvt. Ltd, Mumbai. Sodium bi Carbonate, Talc, Microcrystalline cellulose,Magnesium stearate and Talc was obtained as a gift sample from S.D.Fine Chem. Ltd., Mumbai. Other chemicals and solvents were purchased from analytical grade.

METHODS

Preparation of Verapamil Hydrochloride Floating Matrix Tablet:

Direct compression method:

Verapamil Hydrochloride floating matrix tablets can be prepared by direct compression method. It consists of 3 steps.

- Milling
- Mixing
- Compression

The drug was mixed with the polymers and other ingredients in weight proportion The powder blend is then lubricated with Magnesium stearate (1% w/w) and Talc (1% w/w), and this lubricated blend was compressed into tablets using suitable flat-face round tooling on a single punch tablet compression machine (Cadmach, Ahmadabad, India).

FORMULATION

EVALUATION PARAMETERS

1. Bulk density:

Bulk density of a compound varies substantially with the method of crystallization, milling formulation. Bulk density is determined by pouring presieved granules into a graduate cylinder via a large funnel and measure the volume and weight. (Values are given in Table No: 6)

$$\text{Bulk density} = \frac{\text{weight of granules}}{\text{Bulk volume of granules}}$$

2. Tapped density:

Tapped density is determined by placing a graduated cylinder containing a known mass of granules and mechanical tapper apparatus, which is operated for a fixed number of taps until the powder bed volume has reached a minimum volume. Using the weight of the granules in the cylinder and this minimum volume, the tapped density may be computed. (Values are given in Table No: 6)

$$\text{Tapped density} = \frac{\text{weight of granules}}{\text{Tapped volume of granules}}$$

3. Angle of Repose:

The manner in which stresses are transmitted through a bead and the beads response to applied stress are reflected in the various angles of friction and response. The most commonly used of this in angle of repose, which may be determined experimentally by number of methods. The method used to find the angle of repose is to pour the powder a conical on a level, flat surface and measure the included angle with the horizontal. (Values are given in Table No: 6)

$$\tan\theta = h/r$$

Where h= height of the heap, r= Radius of the heap

2. Carr's Index:

Carr's Index is measured using the values of bulk density and tapped density.
(Values are given in Table No: 6). The following equation is used to find the Carr's Index,

$$CI = \frac{(TD-BD) \times 100}{TD}$$

Where, TD = Tapped density
BD = Bulk density

4. Hausner's Ratio:

It indicates the flow properties of the powder and ratio of Tapped density to the Bulk density of the powder or granules. (Values are given in Table No: 6)

Hausner's Ratio = Tapped density/Bulk density

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6. Thickness or dimension test:

The thickness of the tablets was measured using Digital Vernier Caliper. It is expressed in mm. (Values are given in Table No: 7)

7. Hardness test:

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of tablets was determined by using Monsanto hardness tester, it is expressed in kg/cm^2, three tablets were randomly picked and hardness of tablets was determined. (Values are given in Table No: 7) (Jain sk *et al*., 2006).

Limits: 4 – 10 kg/cm^2

8. Friability test:

Friability of the tablets was determined by using Roche friabilator, it is expressed in %. Ten tablets were initially weighed and transferred to friabilator. The friabilator is operated at 25 rpm for 4 min or run upto 100 revolutions, the tablets were weighed again. The % friability of tablets was calculated. (Values are given in Table No: 7) (Patel DM *et al*., 2007).

The Friability of tablet should not exceeds 1%

$$F = \frac{\text{Initial Wt} - \text{Final Wt}}{\text{Initial Wt}} \times 100$$

9. Weight variation test:

Ten tablets were selected randomly from each batch and weighed individually to cheek for weight variation. A little variation is allowed by U.S pharmacopeia. The following % deviation in weight variation is allowed. (Values are given in Table No: 7)

10. Drug content:

Weigh and powder 20 tablets, weighed accurately a quantity of the powder equivalent to 0.1 gm of verapamil hydrochloride. Shake with 150 ml of 0.1M Verapamil Hydrochloride to produce 200ml and filter. Dilute 10ml of the filtrate to 100ml with water and measure the absorbance of the resulting solution at the maximum at 278nm. Calculate the content of the **Verapamil Hydrochloride taking 118 as the value of a (1% 1cm) at the maximum at about** 278nm. (Values are given in Table No: 7) (Gambhir MN *et al*., 2007).

11. Invitro buoyancy study:

The in vitro buoyancy is characterized by floating lag time and total floating time. The test was performed using USP 24 type II paddle apparatus using 900 ml of 0.1 N HCl at paddle rotation of 50 rpm at 37±0.5 ^{0}C. The time required for tablet to rise to surface of dissolution medium and duration of time the tablet constantly float on dissolution medium was noted as floating lag time and total floating time. (Values are given in Table No: 8) (Baumgartner S *et al*., 2000).

12. Swelling index:

` The swelling behavior of dosage form is measured by studying its weight gain or water uptake. The dimensional changes could be measured in term of increasing tablets diameter or thickness over time. Water uptake is measured in terms of % weight gain as given by equation. (Values are given in Table No: 9, Fig No: 1) (RD kale *et al*., 2007).

$$S_{wt} = \frac{Ws - W_d}{W_d} \times 100$$

Ws - Weight of swollen matrix system

W_d - Weight of dry matrix system

13. In vitro drug release study:

The In-Vitro drug release was performed using USP 24 type II paddle apparatus using 900 ml of 0.1 N HCl at paddle rotation of 50 rpm at 37±0.5 ^{0}C. The samples were withdrawn at predetermined time intervals for a period of 12 hours and replaced with the fresh medium. The samples were filtered through 0.45 mm membrane filter, suitably diluted and analyzed at 278 nm using double beam UV/Vis spectrophotometer (Shimadzu Corporation, UV-1601, and Japan). The content of the drug was calculated using equation generated from standard calibration curve. (Values are given in Table No: 10, Fig, No: 2) (SC Basak *et al*., 2007).

14. Evaluation studies were compared with Marketed product:

The promising formulation F1 was found by evaluation studies were compared with Marketed product (Isoptin 120mg SR tablets) the evaluation parameters were determined and compared with In-Vitro drug release profile. (Values are given in Table No: 11, Fig, No: 3)

RESULTS & DISCUSSION

EVALUATION PARAMETERS

The values obtained for angle of repose for all the formulations are tabulated in table the values were found to be in the range from 24°.47′ to 27°.84′.This indicates good flow property of the powder blend. Bulk density and Tapped density values are within the limits, indicating that the powder blends have the required flow property for direct compression. The Compressibility index values and Hausner's ratio ranges between 25% to 34.2% and 1.12 to 1.2 indicating that the powder blends have the required flow property for direct compression.

Tablet mean thickness was almost uniform in all the formulations and was found to be in the range of 0.520mm to 0.522mm. As the proportion of polymers

increases, the hardness of the tablets was found to increase in the case of hydroxyl propyl methyl cellulose. Methyl cellulose tablets are less harder and thickest tablets. Friability values were found to be less than 1% in all the cases and considered to be satisfactory. Tablets passed weight variation test as the % weight variation was within the pharmacopoeia limits. The weight of the all the tablets was found to be uniform with low standard deviation values. Drug content of all the batches was within the acceptable range which shows proper mixing of the drug with the excipients.

To provide good floating behavior in this stomach, the density of the dosage form should be less than that of gastric contents (1.004gr/cm³). All the batches showed density less than that of gastric fluid (1.004gr/cm³).When the tablet contacts the test medium, the tablet expands (because of swellable polymers) and there was liberation of CO_2 gas (because of effervescent agents, citric acid and sodium bicarbonate) The density decreased due to this expansion and upward force of CO_2 gas generation. This plays an important role in ensuring the floating capability of the dosage form. As the concentration of the polymer increases, the floating lags time decreases.

As the polymer proportion is increased, floating time also increases. Methyl cellulose and the combination of methyl cellulose and hydroxy propyl methyl cellulose formulations were found to have floating characters for a longer period.

The extent of swelling was found by measuring the thickness of the tablet before and after five hours immersed the tablet in 1.2pH buffer. Formulation F3 (1:1 drug: HPMC K4M) tablets were found to swellen more and Formulation F1 (1:0.5 drug: HPMC K4M) tablets were found to be swellen to lesser extent. The thickness of the polymer had major influence on swelling process, matrix integrity as well as floating capability.

In-Vitro Release studies:

The In vitro drug release profile of tablets from each batch (F1 to F8) was carried with 0.1N HCL having pH 1.2, for 8 hours by using paddle type device. From the In-Vitro dissolution data, it was found that the drug release from formulation containing HPMC K4M, the cumulative % of drug release was 95.13 % respectively. The formulation containing HPMC K15M, the cumulative % of drug release was 89.5 % .While the formulation containing both the polymers (HPMC K4M & HPMC K15M) the cumulative % of drug release was 85.6%.

The % drug release was found to be 95.13 % for formulation F1, The marketed product was found to be 92.25 % of drug release in 8 hours of dissolution study. The formulation F1 with 95.13 % of drug release has better control over release of drug was compared with marketed product.

Table No: 1:-Formulation of different batches of Verapamil Hydrochloride Floating Matrix Tablet

S.No	Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
1	**Verapamil HCl**	120	120	120	120	120	120	120	120
2	**HPMC K4M**	60	90	120	----	----	30	60	30
3	**HPMCK15M**	----	----	----	60	90	30	30	60
4	**MCC**	162	132	102	162	132	162	132	147
5	**Sodium bicarbonate**	22.80	22.80	22.80	22.80	22.80	22.80	22.80	22.80
6	**Citric acid (2%)**	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6
7	**Magnesium stearate (1% w/w)**	3.8	3.8	3.8	3.8	3.8	3.8	3.8	3.8
8	**Talc (1% w/w)**	3.8	3.8	3.8	3.8	3.8	3.8	3.8	3.8
9	**Total weight (mg)**	380	380	380	380	380	380	380	380

Table No: 2 Angle of Repose I.P limits

S.No	Angle of Repose	Powder flow
1	< 25	Excellent
2	25 – 30	Good
3	30 – 40	Passable
4	> 40	Very poor

Table No: 3 Carr's Index I.P limits

S.No	Carr's Index	I.P Limits value
1	Excellent	<10
2	Good	11 – 15
3	Fair	16 – 20
4	Possible	21 – 25
5	Poor	26 – 31
6	Very poor	32 – 37
7	Very very poor	>38

Table No: 4 Hausner's Ratio I.P Limits

S.No	Hausner's Ratio	I.P Limits value
1	Excellent	1.00 – 1.11
2	Good	1.1 – 1.18
3	Fair	1.19 – 1.25
4	Possible	1.26 -1.34
5	Very poor	1.35 -1.45
6	Very very poor	>1.60

Table No: 5 Weight variation test I.P Limits

S.No	Average weight of tablets	% deviation
1	130 or less	± 10
2	>130- <324mg	± 7.5
3	>324 mg	± 5

Table No: 6 Pre Formulation Studies

S.No	Formulation	Angle of Repose	Bulk density (gm/cc)	Tapped density (gm/cc)	Compressibility index (%)	Hausner's Ratio
1	F1	26º.73´	0.536	0.622	32.104	1.15
2	F2	28º.48´	0.762	0.849	28.281	1.26
3	F3	24º.55´	0.696	0.826	25.003	1.17
4	F4	27º.84´	0.652	0.767	27.024	1.18
5	F5	24º.58´	0.571	0.651	29.236	1.13
6	F6	25º.26´	0.449	0.536	31.215	1.16
7	F7	26º.84´	0.578	0.636	30.768	1.17
8	F8	24º.47´	0.631	0.695	34.257	1.15

Table No: 7 Evaluation of Floating Tablet of Verapamil Hcl

S.No	Formulation	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Weight variation (%)	Drug content (%)
1	F1	5.23	6	0.9	1.25 ±0.91	99.8
2	F2	5.24	6	0.7	1.35±0.58	99.7
3	F3	5.22	6	0.8	1.42 ±0.24	99.7
4	F4	5.21	7	0.8	1.398±0.36	99.4
5	F5	5.22	7	0.9	0.96 ±0.56	98.8
6	F6	5.24	8	1.2	0.94± 0.88	99.2
7	F7	5.23	8	0.8	1.14 ±0.79	98.6
8	F8	5.21	8	0.9	1.19 ±0.34	97.6

Table No: 8 Buoyancy study

S.No	Formulation	*Buoyancy log time* (minutes)	Total floating time (hrs)
1	F1	0.35	>14
2	F2	0.55	>16
3	F3	1.15	>20
4	F4	0.45	>16
5	F5	1.10	>18
6	F6	0.40	>16
7	F7	0.50	>18
8	F8	1.20	>20

Table No: 9 Swelling Index

S.No	Formulation	Average Initial Thickness (cm)	Average final Thickness (cm)
1	F1	0.3	0.5
2	F2	0.3	0.7
3	F3	0.3	0.9
4	F4	0.3	0.5
5	F5	0.3	0.7
6	F6	0.3	0.5
7	F7	0.3	0.6
8	F8	0.3	0.7

Table No: 10 Comparative dissolution study of different batches with various ratio's of polymer

S.No	Time in Hrs	% of drug release F-1	% of drug release F-2	% of drug release F-3	% of drug release F-4	% of drug release F-5	% of drug release F-6	% of drug release F-7	% of drug release F-8
1	0	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
2	1	9.476	8.151	7.233	6.046	5.743	5.732	5.735	5.233
3	2	18.752	18.380	17.673	14.584	12.410	13.520	12.150	10.896
4	3	29.431	27.434	26.505	25.096	23.055	24.355	22.955	21.124
5	4	42.760	39.450	37.032	34.211	30.833	32.963	29.843	27.834
6	5	58.255	56.434	54.062	49.188	45.500	47.534	43.540	41.520
7	6	69.752	67.977	65.796	64.292	56.688	58.671	55.668	53.688
8	7	91.485	87.792	83.409	76.684	71.622	73.626	70.622	67.622
9	8	95.130	92.551	90.632	89.069	82.530	85.643	82.341	79.687

Table No: 11 In-vitro drug release profile of Verapamil Hydrochloride from Marketed product (Isoptin SR 120mg tablets) and Formulation F-1

S.No	Time (in hours)	% drug release (Marketed sample)	% drug release (F-1)
1	0	0.000	0.000
2	1	8.251	9.476
3	2	18.280	18.752
4	3	27.334	29.431
5	4	39.340	42.760
6	5	56.630	58.255
7	6	67.374	69.752
8	7	87.692	91.485
9	8	92.251	95.130

Fig.No. 1 Comparison of swelling index of Verapamil Hydrochloride floating tablets for F-1 to F-8 formulations

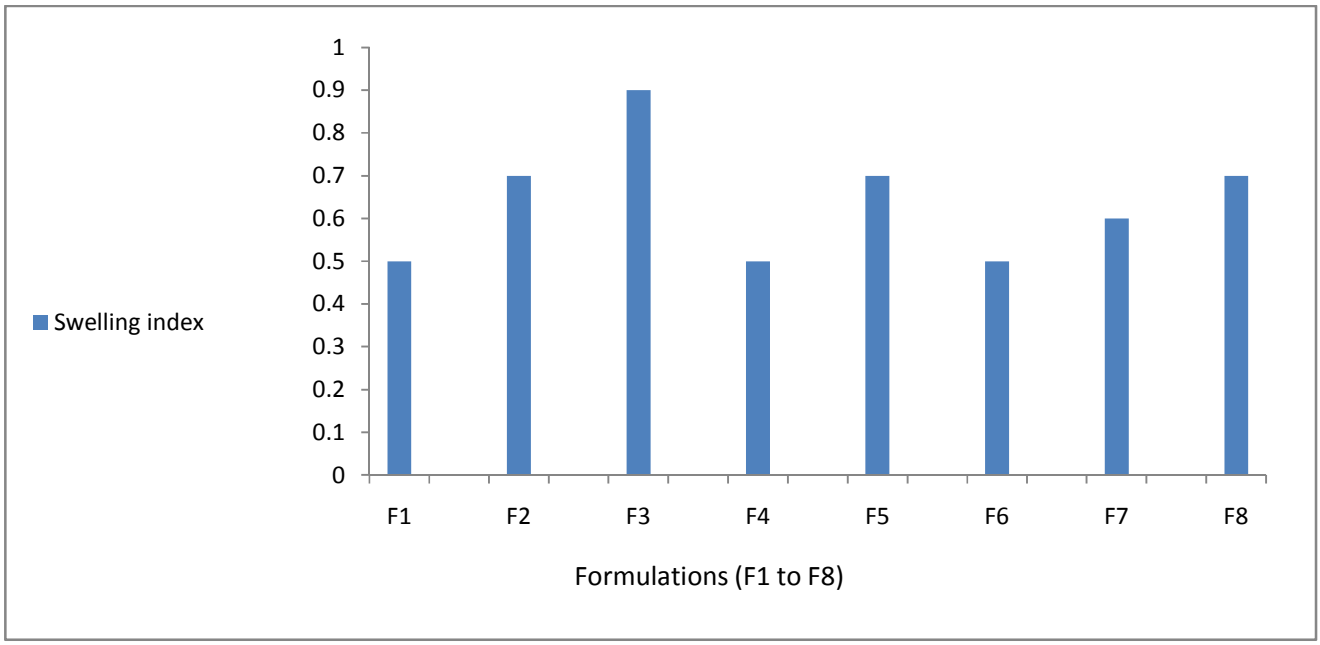


Fig. No.2 Comparative dissolution studies of different batches with various ratios of polymer

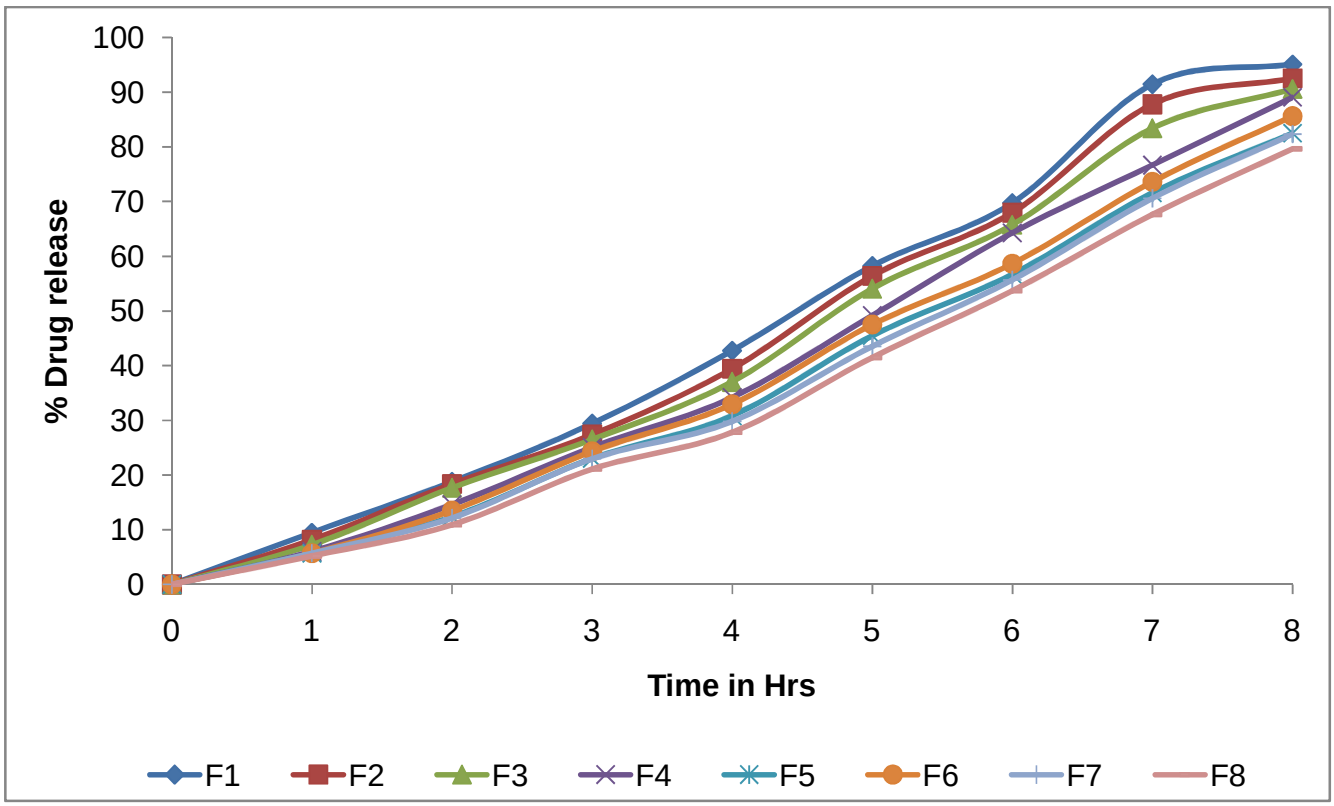
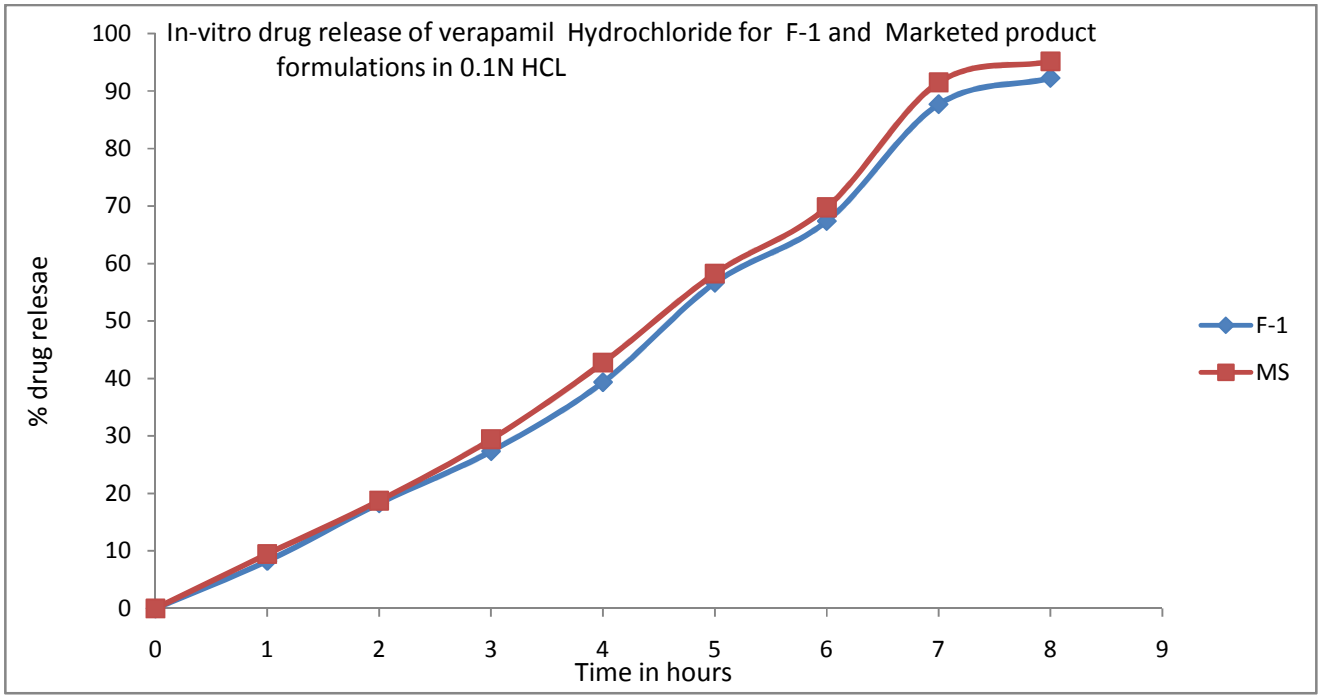


Fig. No.3 In-vitro drug release profile of Verapamil Hydrochloride from Marketed product (Isoptin SR 120mg tablets) and Formulation F-1



The promising formulation F-1 was found by evaluation studies were compared with Marketed product (Isoptin 120mg SR tablets) the evaluation parameters tested and compared with in vitro drug release profile.

CONCLUSION

This research work was done with an aim to design a sustain release oral dosage form of Verapamil Hydrochloride which is a single layer intragastric floating tablet and evaluation of the tablets including in vitro drug release studies. Floating tablets of Verapamil Hydrochloride was prepared by direct compression method. The prepared floating tablets were round in shape. Microscopic examination of tablets from each formulation batch showed circular shape with no cracks. Under pre-formulation studies the organoleptic properties were compiled with the IP specifications. Physical properties such as Bulk density, Tapped density, Angle of repose, Compressibility index and Hausner's ratio was also determined. The Angle of Repose of the drug powder showed passable flow properties. For In-vitro buoyancy and In-vitro drug release, the formulation F-1 (1 :0.5 drug : HPMCK4M) exhibited the maximum floating time and drug release profile similar to that of marketed sustained release dosage form of Verapamil Hydrochloride which meets the requirement of product design. Hence the formulation F-1 was considered as the best formulation and further studies carried out for successful launching of the project. Drug absorption in the gastrointestinal tract is a highly variable procedure and prolonging gastric retention of the dosage form extends the time for drug absorption. Floating drug delivery systems promises to be a potential approach for gastric retention.

REFERENCES

Basak SC, KN Rao, R Manavalan, PR Rao Development and in vitro evaluation of an oral floating matrix tablet formulation of ciprofloxacin. *Indian journal of Pharmaceutical sciences*, 66(3), 2007, 313-316.

Baumgartner S, Kristl J, Vrecer F, Vodopivee P, zorko B. Optimization of floating matrix tablets and evaluation of their gastric residence time. *International journals of Pharmaceutics*, 195, 2000, 125-135.

Brijesh S dev, Avani, Amin, Madhubai. Formulation and invitro release of gastroretensive drug delivery system of Ranitidine hydrochloride. *AAPS pharma science tech*, 31(4), 2010, 1530-1539.

Donald L. Wise Hand book of pharmaceuticals controlled release technology, Marcel dekkar 1st edition, vol-1, 2005, 211-253.

Gambhir MN, Ambade kw, Kurmi SD, kadamVJ, jadav KR. Development and evaluation of oral floating matrix of . diltiazem hydrochloride. *AAPS pharma science tech*. 8(3). 2007, 75-82.

Goodman and gilmans, The pharmacological basics of therapeutics, 11th edition, vol-1, 2010, 832-836.

Jain sk, Agarval gp, Jain nk. Evaluation of porous carrier based floating orlistat microspheres of or gastric delivery. *AAPS pharma science tech*. 7(4), 2006, 91-98.

Kale RD, PT Tayade. A multiple unit floating drug delivery system of piroxicom using eudragit polymer. *Indian Journal Of Pharma Science*, 69, 2007, 120-123.

Krojel and Ronaldbodmeirer. Floating drug delivery system based on coated effervescent cores.International journals of pharmaceutics, , volume-187, issue-2, 1999, 35-42.

Patel DM, Padya NN,Jogini PD.Gastro retentive drug delivery system of carbamazepine. *AAPS pharma science tech*, 8(1), 2007, 45-53.

Reagent and Solution: Indian Pharmacopoeia, vol-2, 2010, 142.

Renald C Rose, Pats Sheskey, Handbook of Pharmaceutical Excipients, 4th edition, vol-1, 2010, 312-314.

Siahi, Jalai, Farnaz, design and evaluation of 1- and 3-layer matrix of Verapamil hydrochloride for sustaining its release. *AAPS pharma science tech*, vol-1,2005, 1-6.

Sungthongjee S, O Peeratakal, Limmatvapitat. Preparation and evaluation of multi unit floating drug delivery system based on gas forming agents. International Journals of Pharmaceutics, 324(2), 2006, 1-7.

Vyas SP, Roop KK Har. Controlled Drug Delivery Concepts and Advances, 1, 2007, 196-217.