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Original Article

Development of monolayer elementary osmotic tablet of verapamil hydrochoride

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ABSTRACT

The purpose of this study was to develop a monolayer elementary osmotic tablet of Verapamil Hydrochloride. The drug candidate selected under the study is Verapamil hydrochloride, a calcium channel blocking agent used in the treatment of angina pectoris, hypertension and cardiac arrhythmia. Verapamil Hydrochloride has a short elimination half-life; this will bring down its dosing frequency to once a day and on the same time make a zero order release system. Tablets were prepared by using controlled release polymers. The formulations were evaluated for pharmacopoeial quality control tests and all the physical parameters evaluated were within the acceptable limits. Formulation M12 was proved to be good drug content, dimensional stability and drug release up to 24 h as compared to the other formulations. Stability studies were carried out on the optimized formulation M12 for period of 3 months at 40^0c/75 %RH. Finally it was observed that there was no change in physiochemical and physical properties as well as in drug release profile even after storage at 45 °C and 75 % for three months.

Key words: Verapamil hydrochloride, dimensional stability, elementary osmotic tablet, stability study.

INTRODUCTION

Osmotic systems use osmotic pressure as driving force intended for controlled delivery of drugs. Elementary osmotic pump [EOP], which is in its simplest design, consists of an osmotic core [containing drug with or without an osmagent] and further coated with a semipermeable membrane [SPM]. The dosage form, following coming in contact with the aqueous fluids, imbibe water at a rate determined by the fluid permeability to the membrane and osmotic pressure of core formulations.[1] These osmotic imbibitions of water consequences in formation of a saturated solution of drug inside the core, which is dispense at controlled rate from the release orifice in the membrane.

While 60 to 80% of drug is released at a steady rate from EOP, a lag time of 30 to 60 minutes is observed in the majority of the cases as the system hydrates previous to zero order delivery from the system begin.[2] These technologies are suitable for delivery of drugs have moderate water solubility. Push pull osmotic pumps [PPOP] can be used for delivery of drugs have extremes of water solubility. It is a bilayer tablet covered by a SPM. A drug along with an osmagent is present in the upper section whereas lower section consists of polymeric osmotic agents.[3-4] The drug section is linked to the outer surface environment via a delivery orifice. Following coming in contacts with the aqueous surroundings, polymeric osmotic layer swell and pushes the drug layer, thus delivering the drug in the form of fine dispersion via the orifice.[5] Different modifications are available for this class of technology like, delayed push pull system [as used in Covera HS, CR formulation for Verapamil], multi layer push pull system [for delayed or pulsatile drug delivery] and push stick system [for delivery of insoluble drugs require high loading, with an elective pulsatile, patterned, or delayed release profile]. OROS CT is used as a once or twice a day formulation for drugs targeted delivery to the colon.[6]

The drug candidate selected under the study is Verapamil hydrochloride, a calcium channel blocking agent used in the treatment of angina pectoris, hypertension and cardiac arrhythmia. Its

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biological half life is 4 to 6 hours and its usual dose is 40 to 120mg three times a day.[7-8] Because of the high frequency of administration and short biological half life, Verapamil hydrochloride is an ideal drug in designing controlled release formulation.

Most cardiovascular measures are prone to takes place in the early on mornings hrs with the renewal of daily activities and this is accompanied by different neurohumoral stimuli information of the circadian variations paves the system to designing antianginal drugs with an proper pharmacokinetic outline that ensures efficient plasma concentration and constant antiischemic and cardio protective result.

MATERIAL AND METHODS

Material: Verapamil hydrochloride was a kind gift from Sidmak laboratories, Gujarat. Magnesium Stearate, lactose, polyvinyl pyrolidone (PVP K30), ethyl cellulose, mannitol, sodium chlorid were purchased from Signet India Pvt. Ltd, Mumbai. HPMC K15M, Carbopol 71G and Isopropyl alcohol (IPA) were purchased from Loba Chemicals, Mumbai. Other excipients used were of standard pharmaceutical grade.

Methods

Formulation of Monolayer Osmotic Tablets of Verapamil hydrochloride: Verapamil hydrochloride, HPMC K15M and Lactose mono were dry mixed. PVP K30 was dissolved in IPA with stirring. Dry mix blend was granulated with prepared binder solution. Wet mass was dried at 50°C in oven. Dried granules were passed through 20# sieve. Above sized granules were mixed with Carbopol 71G, sodium chloride and talc for 10 minutes at 24 rpm in a blender. The above granules were lubricated with 60# passed Magnesium stearate for 5 minutes at 24 rpm in a blender and then lubricated granules were compressed using 9.0 mm, round, standard concave punches, and plain on both the sides in rotary compression machine. Coating solution was prepared by dissolving ethyl cellulose and dibutyl cebecate (75:25) in a mixture of ethanol and acetone (50:50) with constant stirring. Core tablets were coated with prepared coating solution using conventional coating pan machine. The average weight of tablet was checked periodically to achieve the desired target weight gain. The coated tablets were dried at 50°C for 30 min in conventional coating pan at 1-2 rpm. One orifice with a diameter of 0.5 mm was drilled on either side of coated tablet using a microdrill.[9]

Evaluation of granules

Angle of repose: Granules flowability was determined by calculating angle of repose by funnel technique. A funnel with 10 mm inner diameter of stem was fixed at a height of 2 cm above the platform. About 20 g of granules was slowly passed along the wall of funnel till the tip of the pile produced and touches the stem of the funnel. A rough circle was drawn about the pile base and the radius of the sample cone was measured.[10] Angle of repose was calculated from average radius using formula:

$\theta = \tan^{-1} (h/r)$

Where,

θ = angle of repose

h = height of the pile

r = average radius of the powder cone.

Bulk Density: Apparent bulk density of granules was determined by the graduated cylinder and measuring the volume and weight "as it is".[11]

Tapped Density: Tapped density was determined with the aid of tapped density tester apparatus. In this method 20 gm of sample was poured gently through a glass funnel in to a 100mL graduated cylinder. The cylinder was then placed in the apparatus and parameters were set to carry out the test.[11]

Hausner ratio: It provides an indication of the degree of densification which could result from vibration of the feed hopper. Hausner ratio closer of less than 1.25 indicates good flow, while greater than 1.5 indicates poor flow materials.[12]

Carr's index or % compressibility

Carr's index or % compressibility [12] was calculated by using following equations:

$$\text{Carr's index} = \frac{\text{Tapped density - Bulk density}}{\text{Tapped density}} \times 100$$

Evaluation of controlled release osmotic tablets

Tablet thickness and diameter: Tablet Thickness and diameter were accurately measured by using digital vernier caliper in mm.[13]

Hardness and Friability: Hardness of tablet was determined by Monsanto hardness tester. Friability test was done by Roche friabilator. Ten tablets were weighed and were subjected to the combined effect of attrition and shock by utilizing a plastic chamber that revolve at 25 rpm dropping the tablets at distance of 6 in. with each revolution. Operated for 100 revolutions, the tablets were de dusted and reweighed.[14] The percentage friability was calculated.

$$F = \frac{W1 - W2}{W1} \times 100$$

Where F represents the percentage weight loss, and W1 and W2 are the initial and final tablet weights, respectively.

Weight variation: Twenty tablets were selected at random and average weight was determined. Then individual tablets were compared with the average weight.[14] Twenty tablets were weighed and powdered. Powder equivalent to the 0.1gm of the drug was shaken with 150mL of 0.01N HCl for 10 minutes. Enough amount of 0.01 N HCl was added to make 200mL and filtered. 10mL of the filtrate diluted to 100mL through water and the resultant solution absorbance was measured at 278nm.

Orifice diameter size: The orifice diameter of 10 intact tablets was calculated using a Digital Vernier Calliper [Mitutoyo CD 6"CS] and the average value was reported.[15]

***In vitro* dissolution study:** The test was carried out in a rotating basket method specified in the USP XXIII dissolution tester [Electrolab, TDT-08L, India] at a rotation speed of 50 rpm in 900 mL dissolution medium at 37±0.5°C in media with pH 1.2 [HCl 0.1 N] for 2 hr and pH 7.4 [phosphate buffer], till the ending of the test, respectively. 5 mL aliquots of the dissolution fluid were removed at particular time intervals and replaced through new dissolution medium and assayed for the amount of Verapamil hydrochloride by spectrophotometer [JASCO V630, Japan] at wavelength 278 nm. The dissolution data was analyze to calculate % drug released at various time intervals.[16]

Accelerated stability study of optimized formulations: Accelerated stability study was carried out for optimized formulations, to assess its stability as per ICH guidelines. The optimized formulation were wrapped in the laminated aluminum foils and was placed in the accelerated stability chamber (6CHM-GMP, Remi Instrument Ltd., Mumbai) at elevated temperature and humidity conditions of 40^0C/ 75% RH and a control sample was placed at an ambient condition for a period of three months. Sampling was done at a predetermined time of initial 0, 1, 2 and 3 months interval respectively. At the end of study, samples were analyzed for the drug content, *in vitro* drug release profile and other physicochemical parameters.[17-19]

RESULT AND DISCUSSION

The present research work was meant for formulating a solid dosage form system that is tablets for Verapamil hydrochloride by using the principles of osmosis which will bring downward its dosing frequency to once a day and at the similar time produce a zero order release system. It was designed to formulate osmotic drug delivery system that is Monolayer osmotic Tablets (Elementary osmotic pump).

A monolayer osmotic tablet was prepared by coating the core tablet [containing 120 mg of drug and osmogen] with a semipermeable membrane to allow the penetration of water and drilling an orifice which would allow the release of drug following development of suitable osmotic pressure. For preparing a monolayer osmotic tablet, at first core and coating probability trials were carried out to choose the best formulation.

Granules evaluation: The physical characteristics of the granules (M1 to M16) such as bulk density, tapped density, carr's index, hausner ratio, angle of repose were determined. The results are given in Table 3. The bulk densities were ranged from 0.812-0.987 gm/ml. The tapped densities were ranged from 0.829-0.968 gm/ml. The carr's compressibility index were ranged from 10.04-19.56%. The hausners rations were found to be in the limit 1.08-1.26. The angles of repose of all formulation were found to be between the limit 21.19°-26.43°. All the formulation shows excellent flow properties. So, the granules pass the evaluated tests and subjected to after that stage of work compression.

Tablet thickness and diameter: The thickness of the tablets range from 5.42-5.64 mm respectively. The diameter of the tablet in the range of 8.97-9.03mm. There was no variation in tablet thickness and diameter between the formulations. The results are given in Table 4.

Hardness, friability and weight uniformity of tablets: The hardness of the tablets was within the range and optimum for controlled release, and ranging from 6.8-8.0 Kg/cm^2 for all M1-M16 formulations. The friability of all formulations was ranging from 0.088-0.229 % w/w and passes as per IP limit should not be more than 1 % w/w. The weight uniformity of tablet in all formulation was observed to be within the IP limit 10 %. All formulations were complying with the official test. The values were mentioned in Table 4 and Table 5.

Drug content: The assays of all formulation from M1-M16 were found to be between 99.10-99.99 %. The result shows that all formulation containing drug were within the limit. The values were mentioned in Table 5.

Orifice diameter: The orifice diameters of all formulation from M1-M16 were found to be between 0.51-0.56mm. The result shows that all formulation were within the limit. The values were mentioned in Table 5.

***In vitro* drug release study of Monolayer osmotic experimental trial batches:** *In vitro* drug release study was conducted in pH 1.2, and 7.4 simulated to stomach, small intestine respectively. Results shown in Table 6 and 7.

Accelerated stability study: Verapamil hydrochloride optimized formulation M12 was found to be stable during accelerated stability studies for drug content 99.64, 99.26, 99.12 and 99.07% at 0, 1, 2 and 3 months respectively at 40^0c/75% RH. *In vitro* drug release studied for 12 h was found to be 96.63, 95.28, 94.98 and 93.82% at 0, 1, 2 and 3 months respectively at 40^0c/75% RH. Results obtained were shown in Table 8. Finally it was observed that there was no change in physiochemical and physical properties as well as in drug release profile even after storage at 45 °C and 75 % for three months. It may be inferred that there was no degradation of physical properties and change in the matrix system of the formulation.

CONCLUSION

Verapamil hydrochloride is calcium channel blocker used in the treatment of angina pectoris, hypertension and cardiac arrthymias. Its biological half life is 4-6 hrs and its usual dose is 80-240 mg in divided doses. As of high frequency of administration and small biological half life, Verapamil hydrochloride was measured as a perfect drug for scheming a controlled release formulation. The present research work was meant for formulating a solid dosage form system [tablets] for Verapamil hydrochloride by using the principles of osmosis which will bring downward its dosing frequency to once a day and at the similar time produce a zero order release system. Thus the present research study concludes that the Verapamil hydrochloride Monolayer osmotic Tablets (Elementary osmotic pump) could be good option with novelty and target release was observed by good correlation between *in vitro* and *in vivo* radio imaging and pharmacokinetic study. Thus, the designed formulation can be considered as one of the promising formulation techniques.

Table 1: Composition of Monolayer Osmotic Tablets M1-M8 (all quantities in mg)

Formulation code	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**
Verapamil hydrochloride	120	120	120	120	120	120	120	120
HPMC K15M	50	75	100	75	75	75	75	75
Carbopol 71G	50	50	50	75	100	125	75	75
NaCl	50	50	50	50	50	50	75	100
Mannitol	-	-	-	-	-	-	-	-
PVP K30	15	15	15	15	15	15	15	15
Lactose	195	170	145	170	145	120	120	95
Magnesium stearate	10	10	10	10	10	10	10	10
Talc	10	10	10	10	10	10	10	10
Coating % weight gain	5	5	5	5	5	5	5	5

Table 2: Composition of Monolayer Osmotic Tablets M9-M16 (all quantities in mg)

Formulation code	**M9**	**M10**	**M11**	**M12**	**M13**	**M14**	**M15**	**M16**
Verapamil hydrochloride	120	120	120	120	120	120	120	120
HPMC K15M	75	75	75	75	75	75	75	75
Carbopol 71G	75	75	75	75	75	75	75	75
NaCl	-	-	-	50	50	50	50	50
Mannitol	50	75	100	50	50	50	50	50
PVP K30	15	15	15	15	15	15	15	15
Lactose	145	120	95	95	95	95	95	95
Magnesium stearate	10	10	10	10	10	10	10	10
Talc	10	10	10	10	10	10	10	10
Coating % weight gain	5	5	5	5	7	10	12	15

Table 3: Evaluation of monolayer osmotic tablets granules (M1-M16)

Formulation code	Bulk density gm/ml	Tapped density gm/ml	Carr's index (%)	Hausner's ratio	Angle of repose (°)
M1	0.832	0.950	16.97	1.14	22.68
M2	0.823	0.946	17.39	1.15	22.30
M3	0.816	0.951	18.91	1.26	24.15
M4	0.921	0.840	15.58	1.18	23.68
M5	0.886	0.956	11.38	1.13	25.39
M6	0.987	0.843	10.09	1.09	24.16
M7	0.805	0.965	19.45	1.23	21.19
M8	0.812	0.961	18.29	1.25	25.61
M9	0.946	0.829	10.04	1.08	26.43
M10	0.918	0.861	17.71	1.22	23.61
M11	0.847	0.965	16.70	1.19	24.68
M12	0.816	0.958	19.56	1.21	24.72
M13	0.837	0.968	18.11	1.24	23.14
M14	0.817	0.949	18.60	1.23	24.71
M15	0.814	0.953	19.32	1.21	25.05
M16	0.847	0.965	16.70	1.19	23.68

Table 4: Evaluation of monolayer osmotic tablets (M1-M16)

Formulation code	Thickness in mm	Diameter in mm	Hardness in Kg/cm^2	Friability in % w/w
M1	5.64	9.03	7.1	0.130
M2	5.46	9.01	7.2	0.128
M3	5.57	9.00	7.4	0.088
M4	5.56	8.99	7.1	0.229
M5	5.42	8.98	7.3	0.164
M6	5.47	9.00	7.2	0.165
M7	5.56	9.03	8.0	0.173
M8	5.61	9.01	7.2	0.149
M9	5.62	9.02	7.1	0.121
M10	5.60	9.00	6.9	0.094
M11	5.45	8.99	6.8	0.083
M12	5.57	8.97	6.9	0.168
M13	5.53	8.99	7.1	0.148
M14	5.60	8.98	7.2	0.088
M15	5.48	8.98	7.0	0.154
M16	5.53	9.03	7.4	0.123

Table 5: Evaluation of monolayer osmotic tablets (M1-M16)

Formulation code	Weight variation in mg	Drug content (%)	Orifice diameter mm
M1	509.20	99.61	0.51
M2	502.71	99.49	0.53
M3	495.32	99.89	0.52
M4	466.05	99.10	0.55
M5	499.02	99.37	0.56
M6	505.53	99.39	0.52
M7	496.78	99.54	0.51
M8	498.44	99.36	0.56
M9	500.05	99.89	0.53
M10	503.71	99.99	0.55
M11	505.40	99.12	0.51

M12	501.82	99.27	0.54
M13	505.73	99.83	0.54
M14	503.66	99.42	0.55
M15	504.91	99.51	0.53
M16	502.71	99.39	0.57

Table 6: Cumulative % drug release of monolayer osmotic tablet (M1-M8)

Time	**Cumulative % drug release**							
(h)	M1	M2	M3	M4	M5	M6	M7	M8
0	0	0	0	0	0	0	0	0
1	7.08	10.74	9.42	3.84	7.65	13.16	13.89	11.95
2	12.16	19.68	17.53	9.37	13.46	19.68	19.35	17.49
4	27.71	32.81	32.58	22.47	25.36	27.96	31.54	26.64
6	44.06	41.28	43.72	31.58	38.89	32.61	42.87	35.62
8	54.92	50.93	52.85	40.72	49.74	43.61	54.95	46.84
10	68.27	66.19	63.30	54.57	62.58	52.37	69.72	54.09
12	71.61	72.64	74.64	63.92	77.63	61.65	77.48	68.37
16	89.47	90.38	81.92	73.94	89.47	79.52	86.69	82.36
24			89.38	93.26	91.68	85.32	94.04	91.99

Table 7: Cumulative % drug release of Monolayer osmotic tablet (M9-M16)

Time	**Cumulative % drug release**							
(h)	M9	M10	M11	M12	M13	M14	M15	M16
0	0	0	0	0	0	0	0	0
1	6.18	11.72	8.23	5.41	4.61	3.62	3.09	3.52
2	11.19	18.62	16.32	8.31	11.63	10.64	10.27	10.93
4	24.77	30.14	31.86	21.72	20.16	21.61	21.42	20.24
6	43.56	42.26	41.25	34.83	31.92	30.18	32.97	32.24
8	53.12	51.65	55.29	44.28	43.42	41.18	42.05	40.82
10	63.57	67.17	66.09	56.77	55.74	53.72	49.91	44.93
12	72.62	74.62	75.16	65.81	67.32	64.54	57.34	58.77
16	86.42	91.88	83.27	72.46	69.76	69.02	66.74	62.36
24			93.37	96.63	92.85	89.25	84.94	81.87

Table 8: Results of Accelerated stability study of optimized formulations

	Optimized formulation	
	Drug content (%)	**% drug release**
Initial	99.64	96.63
One month		
Ambient	99.54	95.79
40^0c / 75%RH	99.26	95.28
Two month		
Ambient	99.20	94.47
40^0c / 75%RH	99.12	94.98
Three month		
Ambient	99.09	93.38
40^0c / 75%RH	99.07	93.82

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