Research Article
AMERICAN JOURNAL OF PHARMACY AND HEALTH RESEARCH
www.ajphr.com
2014, Volume 2, Issue 12
ISSN: 2321–3647(online)

Development and *In-Vitro* Evaluation of Bilayer Elementary Osmotic Tablet of Verapamil Hydrochoride

Sancheti Vikram Nirmal[1]*, ChordiyaMayur Ashok[2], K. Senthilkumaran[3]
1. Department of Pharmaceutics, Padmavathi College of Pharmacy & Research Institute, Dharmapuri, Tamil nadu, India.
2. Department of Pharmaceutics, SNJBs SSDJ College of Pharmacy, Chandwad, Nashik, India.
3. Department of Pharmaceutics, K.K. College of Pharmacy, Chennai, India.

ABSTRACT

The purpose of this study was to develop a bilayer 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 B12 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 formulationB12 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.

Keywords: Verapamil hydrochloride, dimensional stability, elementary osmotic tablet, stability study.

*Corresponding Author Email vikram.sancheti@gmail.com
Received 16 November 2014, Accepted 28 November 2014

Please cite this article as: Sancheti VN *et al.*, Development and *In-Vitro* Evaluation of Bilayer Elementary Osmotic Tablet of Verapamil Hydrochoride. American Journal of Pharmacy & Health Research 2014.

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 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 anti-ischemic and cardio protective result.

MATERIAL AND METHOD

Material

Verapamil hydrochloride was a kind gift from Sidmak laboratories, Gujarat. Magnesium Stearate, lactose, polyvinyl pyrolidone (PVP K30), ethyl cellulose, mannitol, sodium chloride 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 Bilayer Osmotic Tablets of Verapamil hydrochloride

Layer 1 (Drug Layer): Verapamil hydrochloride, HPMC K15M, Lactose mono, NaCl and Mannitol (Osmogens) and FeO (colourant) 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. The above blend was mixed with talc for 5 min at 24 rpm in a blender. This blend was then lubricated with Mg stearate for 5 min at 24 rpm in blender. Layer 2 (Push layer): Carbopol 71G, Sodium chloride, Mannitol, Lactose DCL, PVP K 30 and talc were mixed for 20 minutes at 24 rpm in an blender. The above granules were lubricated with 60# passed Magnesium stearate for 5 minutes at 24 rpm in a blender. The bilayer tablet was compressed using the above prepared blend 1 and blend 2 using a bilayer rotary compression machine. Lubricated granules were compressed using 9.0 mm, round, standard concave punches, 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 weight gain of core tablet. 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 the coloured side of coated tablet[9].

Table 1: Composition of Bilayer Osmotic Tablets B1-B8 (all quantities in mg)

Formulation code	B1	B2	B3	B4	B5	B6	B7	B8
Layer 1 (Drug Layer)								
Verapamil hydrochloride	120	120	120	120	120	120	120	120
HPMC K15M	50	75	25	50	50	50	50	50
NaCl	50	50	50	50	50	50	75	25
Mannitol	-	-	-	-	-	-		
PVP K30	10	10	10	10	10	10	10	10

Lactose	58	33	83	58	58	58	33	83
Magnesium stearate	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5
Ferric oxide red	2	2	2	2	2	2	2	2
Layer 2 (Push layer)								
Carbopol 71G	50	50	50	25	75	100	50	50
NaCl	50	50	50	50	50	50	75	25
Mannitol	-	-	-	-	-	-		
PVP K30	10	10	10	10	10	10	10	10
Lactose	80	80	80	125	55	30	55	105
Magnesium stearate	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5
Coating % weight gain	5	5	5	5	5	5	5	5

Table 2: Composition of Bilayer Osmotic Tablets B9-B16 (all quantities in mg)

Formulation code	**B9**	**B10**	**B11**	**B12**	**B13**	**B14**	**B15**	**B16**
Layer 1 (Drug Layer)								
Verapamil hydrochloride	120	120	120	120	120	120	120	120
HPMC K15M	50	50	50	50	50	50	50	50
NaCl	-	-	-	25	25	25	25	25
Mannitol	25	50	75	25	25	25	25	25
PVP K30	10	10	10	10	10	10	10	10
Lactose	83	58	33	58	58	58	58	58
Magnesium stearate	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5
Ferric oxide red	2	2	2	2	2	2	2	2
Layer 2 (Push layer)								
Carbopol 71G	50	50	50	50	50	50	50	50
NaCl	-	-	-	25	25	25	25	25
Mannitol	25	50	75	25	25	25	25	25
PVP K30	10	10	10	10	10	10	10	10
Lactose	105	80	55	80	80	80	80	80
Magnesium stearate	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5
Coating % weight gain	5	5	5	5	7	10	12	15

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]. Bulk density was calculated by using following formula:

$$\text{Bulk density (g/mL)} = \frac{\text{Weight of sample in grams}}{\text{Volume occupied by the sample}}$$

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 100mLgraduated cylinder. The cylinder was then placed in the apparatus and parameters were set to carry out the test[11]. Volume occupied by the sample after tapping were recorded and tapped density was calculated by following formula:

$$\text{Tapped density (g/mL)} = \frac{\text{Weight of sample in grams}}{\text{After tapping volume occupied by the sample}}$$

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].

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

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].

RESULTS AND DISCUSSION

Granules evaluation

The physical characteristics of the granules (B1 to B16) 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 0.615-0.786 gm/ml. The tapped densities were ranged from 0.641-0.767 gm/ml. The carr's compressibility index were ranged from 10.24-19.26%. The hausners rations were found to be in the limit 1.11-1.29. The angles of repose of all formulation were found to be between the limit 21.39°-26.63°. All the formulation shows excellent flow properties. So, the granules pass the evaluated tests and subjected to after that stage of work compression.

Table 3: Evaluation of Bilayer osmotic tablets granules (B1-B16)

Formulation code	Bulk density gm/ml	Tapped density gm/ml	Carr's index (%)	Hausner's ratio	Angle of repose (θ)
B1	0.662	0.752	16.47	1.24	22.58
B2	0.643	0.742	17.29	1.25	22.40
B3	0.626	0.754	18.61	1.16	24.25
B4	0.741	0.643	15.48	1.28	23.48
B5	0.666	0.753	11.58	1.23	25.29
B6	0.767	0.641	10.69	1.19	24.56
B7	0.615	0.762	19.25	1.13	21.39
B8	0.622	0.662	18.69	1.15	25.71
B9	0.786	0.726	10.24	1.18	26.63
B10	0.729	0.767	17.31	1.12	23.51
B11	0.686	0.762	16.50	1.29	24.78
B12	0.625	0.754	19.26	1.21	24.42
B13	0.668	0.764	18.41	1.14	23.34
B14	0.625	0.745	18.30	1.13	24.41
B15	0.623	0.751	19.22	1.11	25.35
B16	0.625	0.762	16.40	1.29	23.98

Tablet thickness and diameter

The thickness of the tablets range from 5.41-5.67 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.

Table 4: Evaluation of Bilayer osmotic tablets (B1-B16)

Formulation code	Thickness in mm	Diameter in mm	Hardness in Kg/cm^2	Friability in % w/w
B1	5.44	9.02	7.0	0.140
B2	5.66	9.02	7.1	0.138
B3	5.67	9.01	7.2	0.098
B4	5.46	8.98	7.3	0.219
B5	5.52	8.99	7.2	0.124
B6	5.57	9.01	7.4	0.185
B7	5.66	9.02	8.1	0.193
B8	5.41	9.03	7.3	0.159
B9	5.52	9.01	7.2	0.141
B10	5.50	9.01	6.8	0.084
B11	5.65	8.98	6.6	0.089
B12	5.57	8.99	6.7	0.162
B13	5.43	8.98	7.0	0.149
B14	5.50	8.99	7.1	0.082
B15	5.58	8.97	7.2	0.155
B16	5.63	9.02	7.2	0.128

Hardness, friability and weight uniformity of tablets

The hardness of the tablets was within the range and optimum for controlled release, and ranging from 6.6-8.1 Kg/cm^2 for all B1-B16 formulations. The friability of all formulations was ranging from 0.082-0.219 % 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 mentioned in Table 4 and Table 5.

Drug content

The assays of all formulation from B1-B16 were found to be between 99.20-99.99 %. 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 B1-B16 were found to be between 0.51-0.57 mm. The result shows that all formulation were within the limit. The values were mentioned in Table 5.

Table 5: Evaluation of Bilayer osmotic tablets (B1-B16)

Formulation code	Weight variation in mg	Drug content (%)	Orifice diameter mm
B1	508.30	99.81	0.53
B2	503.21	99.69	0.51
B3	496.32	99.79	0.55

B4	496.15	99.20	0.56
B5	498.12	99.47	0.53
B6	500.43	99.69	0.57
B7	497.78	99.64	0.53
B8	499.64	99.86	0.55
B9	501.55	99.99	0.51
B10	502.81	99.59	0.53
B11	503.60	99.32	0.52
B12	502.22	99.57	0.56
B13	504.13	99.53	0.53
B14	502.56	99.32	0.54
B15	503.71	99.31	0.51
B16	501.83	99.89	0.52

In vitro drug release study of Bilayer osmotic experimental trial batches

In vitro drug release study was conducted in pH 1.2, and 7.4 simulated stomach, small intestine respectively. [Table 6 and Table 7]

Table 6: Cumulative % drug release of Bilayer osmotic tablet (B1-B8)

Time (h)	Cumulative % drug release							
	B1	B2	B3	B4	B5	B6	B7	B8
0	0	0	0	0	0	0	0	0
1	12.38	11.74	8.58	9.27	9.40	7.73	8.43	7.14
2	21.85	17.58	16.66	15.72	14.43	10.41	9.71	11.53
4	37.73	32.67	28.04	29.90	23.74	19.73	17.49	19.47
6	49.92	42.92	38.16	41.58	31.48	27.51	30.78	25.73
8	64.17	53.84	46.43	49.38	41.79	38.33	43.82	35.07
10	79.62	76.37	61.79	64.66	56.28	52.71	60.75	52.89
12	87.29	84.76	83.65	78.39	69.31	61.02	83.44	69.30
16	90.78	92.13	89.43	93.15	81.33	74.88	92.09	83.44
24	-	-	-	-	94.93	92.13	-	90.03

Table 7: Cumulative % drug release of Bilayer osmotic tablet (B9-B16)

Time (h)	Cumulative % drug release							
	B9	B10	B11	B12	B13	B14	B15	B16
0	0	0	0	0	0	0	0	0
1	7.63	10.43	18.56	19.69	10.46	8.19	7.04	8.30
2	12.25	18.49	21.69	25.17	17.37	11.25	10.38	11.74
4	23.43	31.26	32.14	32.49	28.54	23.26	23.27	19.29
6	34.90	40.72	43.68	40.84±	41.45	37.50	32.26	28.27
8	46.11	53.95	56.90	59.33	51.93	58.64	44.02	45.24
10	59.65	57.89	62.39	64.52	66.08	72.24	61.15	62.15
12	68.63	68.60	71.68	72.93	79.36	81.85	73.28	76.41
16	76.83	79.18	83.82	82.98	91.53	93.03	85.31	83.44
24	89.61	90.78	91.36	94.92	-	-	-	-

Accelerated stability study

Verapamil hydrochloride optimized formulationB12 was found to be stable during accelerated stability studies for drug content 99.69, 99.61, 99.52 and 99.38% at 0, 1, 2 and 3 months respectively at 40^0C/75% RH. *In vitro* drug release studied for 42 h was found to be 94.92, 94.28, 92.98 and 92.41% 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.

Table 8: Results of Accelerated stability study of optimized formulations

	Optimized formulation	
	Drug content (%)	**% drug release**
Initial	99.69	94.92
One month		
Ambient	99.58	94.73
40^0c / 75%RH	99.61	94.28
Two month		
Ambient	99.48	93.58
40^0c / 75%RH	99.52	92.98
Three month		
Ambient	99.39	93.22
40^0c / 75%RH	99.38	92.41

CONCLUSION

Verapamil hydrochloride is calcium channel blocker used in the treatment of angina pectoris, hypertension and cardiac arrthymis. 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 Bilayer 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.

REFERENCES

1. Theeuwes F. Elementary osmotic pump. J. Pharm. Sci. 1975; 64: 1987-1991.
2. Jerzewski RL, Chien YW. Osmotic drug delivery in: A. Kydonieus (Ed.), Treatise on Controlled Drug Delivery: Fundamentals, Optimization, Application, Marcel Dekker, New York. 1992: 225-253.
3. Wong PSL, Barclay B, Deters JC, Theeuwes F. Osmotic device with dual thermodynamic activity. US patent 4,612,008, Sept. 16, 1986.
4. Cortese R, Theeuwes F. Osmotic device with hydrogel driving member. US patent 4,327,725, May 4, 1982.
5. Swanson DR, Barclay BL, Wong PSL, Theeuwes F. Nifedipine gastrointestinal therapeutic system. Am. J. Med. 1987; 83 (Suppl. 6B): 3-9.
6. Theeuwes F, Wong PSL, Burkoth TL, Fox DA. Osmotic systems for colon-targeted drug delivery, in: P.R. Bieck(Ed.), Colonic Drug Absorption and Metabolism. Marcel Dekker, New York. 1993: 137-158.
7. Martindale, The Extra Pharmacopeia. 33rd edition. 2001: 789-992.
8. USP; The United States Pharmacopeial convention inc., CD-2004; USP 27-NF-22.
9. Lachman L, Liberman HA, Kanig JL. The theory and practice of industrial pharmacy. 3rd ed. Bombay; Varghese publishing house; 1987; 294-342.
10. Fiese EF, Hagen TA. Preformulation In: The Theory and Practice of Industrial Pharmacy. Lachman L, Lieberman HA, Kanig JL. 3rd Ed. Varghese Publishing House. 1990; p. 183-84.
11. Wells JI, Aulton ME. Pharmaceutical Preformulation, In: Aulton's Pharmaceutics, Churchill Livingstone Elsevier., 3rd Ed, p. 355-56.
12. Hausner H. H. Friction condition in a mass of metal powders. Int J Powder Metall. 1967; 3: 713.
13. Khan FN, Dehghan MH. Enhanced bioavailability of atorvastatin calcium from stabilized gastric resident formulation. AAPS Pharm Sci Tech. 2011; 12(4): 1077-1086.
14. Veerareddy PR, Nama M, Gonugunta CR. Formulation and evaluation of gastroretentive dosage forms of clarithromycin. AAPS Pharm Sci Tech. 2008; 9(1): 231-237.
15. Chen C, Lee D, Xie J. Controlled release formulation for water insoluble drugs in which a passageway is formed in situ, US patent 5,736,159, April 7, 1998.
16. Ayer AD, Balkie HH. Method and apparatus for forming a hole in a drug dispensing device, US patent 5,071,607, Dec.10, 1991.

17. Kanvide SA, Kulkarni MS. Stability of oral solid dosage form-A global persective. Phama Times. 2005; 37: 9-16.
18. Banker GS, Rhodes CT. Modern Pharmaceutics. Marcel Dekker; 1979: 203.
19. Schellekens RCA, Stuurman FE, Van der Weert FHJ, Kosterink JGW, Frijlink HW. A novel dissolution method relevant to intestinal behavior and its application in the evaluation of modified release mesalazine products. Eur J Pharm Sci. 2007; 30:15-20.