OPEN ACCESS

Saudi Journal of Medical and Pharmaceutical Sciences
Abbreviated Key Title: Saudi J Med Pharm Sci
ISSN 2413-4929 (Print) | ISSN 2413-4910 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

Original Research Article **Pharmaceutics**

Formulation and Evaluation of Sustained Release Pellets of Verapamil HCL

Devoju Ramya[1*], Dr. M. Sunitha Reddy[1]

[1]Department of Pharmaceutics, Centre for Pharmaceutical Sciences, Institute of Science and Technology, Jawaharlal Nehru Technological University Hyderabad, Kukatpally, Hyderabad, 500085, Telangana, India

DOI: 10.36348/sjmps.2022.v08i10.007 | **Received:** 02.09.2022 | **Accepted:** 11.10.2022 | **Published:** 14.10.2022

***Corresponding author:** Devoju Ramya
Department of Pharmaceutics, Centre for Pharmaceutical Sciences, Institute of Science and Technology, Jawaharlal Nehru Technological University Hyderabad, Kukatpally, Hyderabad, 500085, Telangana, India

Abstract

Verapamil Hydrochloride, an antihypertensive agent which is used as a calcium channel blocker. The aim of the present study was to formulate and evaluate Verapamil HCL sustained release pellets. The work is to obtain Verapamil HCL sustained release pellets by using HPMC based polymers i.e., HPMC AN6, HPMC E5, HPMC E15 in the sustained release layer. The verapamil Hydrochloride has pH-dependent solubility. To overcome the pH dependent solubility Fumaric acid was used that which provides micro-acidic environment. Different Ratios of Ethyl-cellulose and HPMC polymers were used to optimise and evaluate the formulation for the sustained release of the drug. It uses the Pelletization technology. This technique is practised to produce pellets of uniform size with high drug loading capacity and also to prevent the segregation and dust.

Keywords: Calcium channel blocker, sustained release pellets, HPMC, Pelletization technology.

INTRODUCTION

The sustained drug delivery systems are used for prolonged release of the drug to achieve therapeutic effect continuously over an extended period of time. Sustained drug delivery systems reduce the frequency of administration. Sustained release drug delivery system maintains drug release over a sustained period of time but not at a constant rate. Oral drug delivery systems are classified into single unit dosage forms and multiple unit dosage forms. Multiple unit dosage forms include granules and pellets. Pellets can be defined as the agglomerates of fine powder or granules which are small, free flowing, spherical particulates made of drug and pharmaceutical excipients. Pellets offers more technological and pharmacological advantages over conventional dosage forms. sustained release pellets are designed to improve the safety and efficacy of active pharmaceutical ingredient and also offer flexibility in dosage form design and development. Due to free dispersion of pellets in the GI tract, the drug absorption is maximum, and less potential side effects.

OBJECTIVE

The objective of the study was to optimise the concentration of HPMC polymers for sustained release layer coating on the drug loaded pellets.

MATERIALS AND METHODS

Verapamil HCl, Sugar spheres, Fumaric acid, HPMC AN6, HPMC E5, HPMC E15, Talc, Lactose, PVP k30, Ethyl cellulose 45cps, IPA were materials used in the formulation verapamil HCl sustained release pellets.

Experimental work:

Standard curve of verapamil in water:

A stock solution of verapamil (100µg/ml) was prepared by dissolving 10mg of drug in water and final volume was made to 100ml. The solution in concentration range of 5-25µg/ml was prepared by appropriate dilutions of stock solution. The UV absorbances of these solutions were determined spectrophotometrically at λmax 278 nm using double beam UV-Visible spectrophotometer.

FTIR compatibility studies:

The drug- excipient studies were done to verify whether there is interaction between the drug and the excipients. Compatibility studies with excipients was done by FTIR. These studies help in the suitable selection of excipients for formulation. FTIR compatibility uses the KBr pellet method. The pure drug and physical mixtures were made as discs and

their compatibility studies were determined through the FTIR. The spectrum of the pure drug was compared with physical mixture of the drug and excipients that determines the chemical interaction between API and excipients.

The spectrum of the pure drug and the spectrum of the excipients are compared to study and identify any incompatibilities**.**

Preparation of Verapamil sustained release pellets:

Verapamil HCL and fumaric acid were milled. Milled Verapamil API passed through 0.5mm screen for about 1 cycle in a pulveriser. Lactose milled in a pulveriser fitted with 0.5mm screen. Milled fumaric acid in a pulveriser fitted with 0.5mm screen for about 1 cycle.

Sifting

Talc sifted through #60 mesh and Sugar spheres sifted through #30 & #35 mesh. The milled API, Fumaric acid, lactose and sifted talc blended for 5 minutes.

Binder solution preparation

Take the weighed quantity of ethanol in a beaker and kept under continuous stirring. Add the weighed quantity of PVP K30 to the beaker, under continuous stirring until clear solution forms.

Drug layering (stage-1):

Sugar spheres are loaded into a coating pan and the sugar spheres are wetted with the binder solution. The wetted sugar spheres coated with the drug mix (verapamil HCL) with process parameters (Pan RPM-50, Atomic air- 0.5 kg/cm²)

Drying:

The above sifted pellets dried in a tray drier at 50±5°C for about 2 hrs and dry till LOD reaches below 2%w/w.

DRUG LAYERING:

Table 1

S. No	Materials	Quantities
1	Sugar spheres	100 mg
2	verapamil	360 mg
3	Fumaric acid	90 mg
4	Talc	10 mg
5	Lactose	14 mg
Polymeric solution (2% solids		
6	PVP K30	8 mg
7	Ethanol	Q.S.

Take the required quantity of Isopropyl alcohol to which Ethyl cellulose 45cps added and continue stirring till the clear solution has obtained, followed by addition of purified water. Add HPMC to solution of above step under continuous stirring to obtain clear solution.

Take the required quantity of water and added PEG 400 and stir until clear solution formed then this PEG solution is added to EC solution and kept for stirring for 45 minutes and then talc was added.

Load the drug loaded pellets into FBC bowl. Set the inlet temperature 45±5°C to reach the bed temperature of about 35±5°C.

Coat the drug loaded pellets by bottom spray Wurster at peristaltic pump rpm of 0-10 and atomising air pressure of 0.5-1.5 kg/cm² till the target weight gain has been achieved.

After the completion of coating, dry the pellets in FBC for about 15 minutes at given bed temperature of about 35±5°C.

Table 2: Sustained Release Layer Coating

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9
	50:50	60:40	70:30	50:50	60:40	70:30	50:50	60:40	70:30
Ethyl cellulose 45cps	15 mg	18 mg	21 mg	15 mg	18 mg	21 mg	15 mg	18 mg	21 mg
HPMC E5	15 mg	12 mg	9 mg	-	-	-	-	-	-
HPMC 606	-	-	-	15mg	12 mg	9 mg	-	-	-
HPMC E15	-	-	-	-	-	-	15 mg	12 mg	9 mg
PEG 400	3 mg	3 mg	3 mg	3 mg	3 mg	3 mg	3 mg	3 mg	3 mg
Talc	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg
IPA	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S
Purified water	Q.S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S
Total (mg)	620 mg	620 mg	620 mg	620 mg	620 mg	620 mg	620 mg	620 mg	620 mg

EVALUATION OF PELLETS

Particle size distribution

The PSD of the pellets were determined by the simple sieve analysis method. 100 gms of the pellets were taken in to sieve shaker and sieves was placed (#14, #16, #18, #20 and #25) in a series. Sieve shaker was run for 5 minutes, all the sieves were taken out and retained granules were collected by respective mesh and the percentage of cumulative retain pellets was

calculated. The average size of the pellets was determined.

Flow Properties

Bulk density, tapped density, Hausner's ratio and Angle of repose was evaluated. Bulk density and tapped density were determined by using tap density tester. Angle of repose was determined by the fixed funnel method.

Percentage yield

The yield was determined by weighing the pellets and then finding out the percentage yield with respect to the weight of the input materials.

Friability

Pellets mechanical strength was determined friability test. Pellets with good mechanical strength will have lower friability values. Known mass of pellets were taken in granular friabilator and then subjected to friability testing for 4 minutes at 25 rpm.

In-vitro Dissolution studies

The In-vitro drug release studies were carried out using USP type-I dissolution test apparatus (Basket type). The studies were carried out for 360 mg of verapamil drug equivalent sustained release pellets initially for 2 hours in 900ml of 0.1N HCL and pH 6.8 (Phosphate buffer) for remaining 24 hours i.e., 3 to 24 hours at temperature 37±0.5°C. 5ml of aliquots were withdrawn at different time intervals. The withdrawn samples were replaced by its equivalent volume of dissolution medium. The samples were analysed for drug content against 0.1N HCL as blank at λmax 278.0 nm for first 2 hours of sample. The samples collected from phosphate buffer were analysed for drug content against pH 6.8 phosphate buffer as blank for 3 to 24 hours of samples. The percentage drug release was plotted against time to determine release profile.

In vitro drug release kinetic studies

The In vitro drug release kinetic studies of sustained release pellets of verapamil were fitted into five kinetics models. i.e., Zero-order, first-order release kinetics, Hi-guchi plot, Korsemayer-peppas, Hixson-crowell model. These studies were used to determine the pattern of drug release and mechanism.

RESULTS AND DISCUSSION

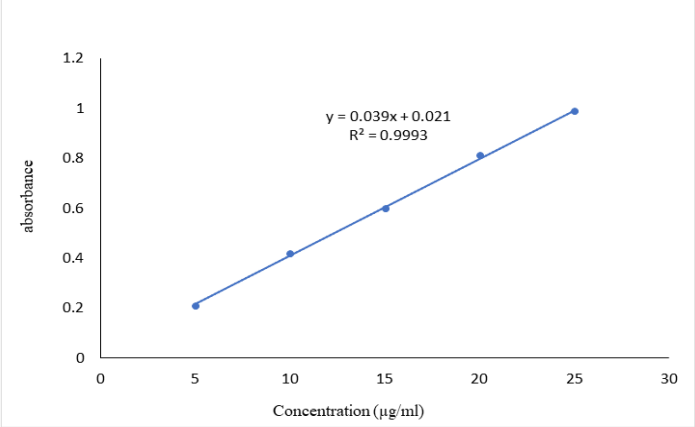

Figure 1: Standard curve of verapamil HCl in water

FTIR compatibility studies:

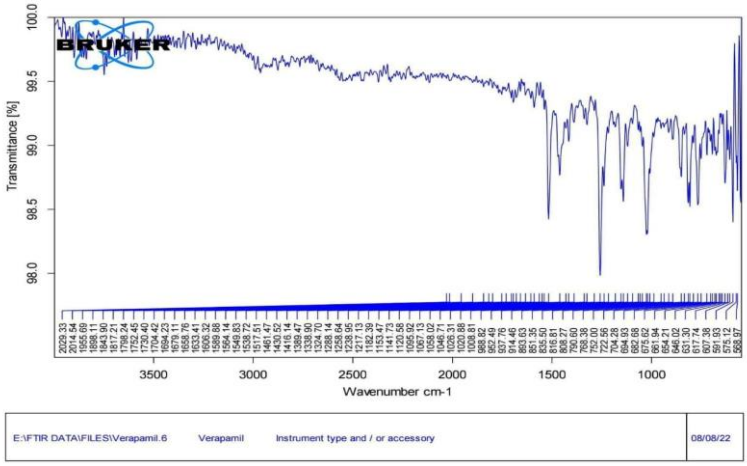

Figure 2: FTIR of Verapamil

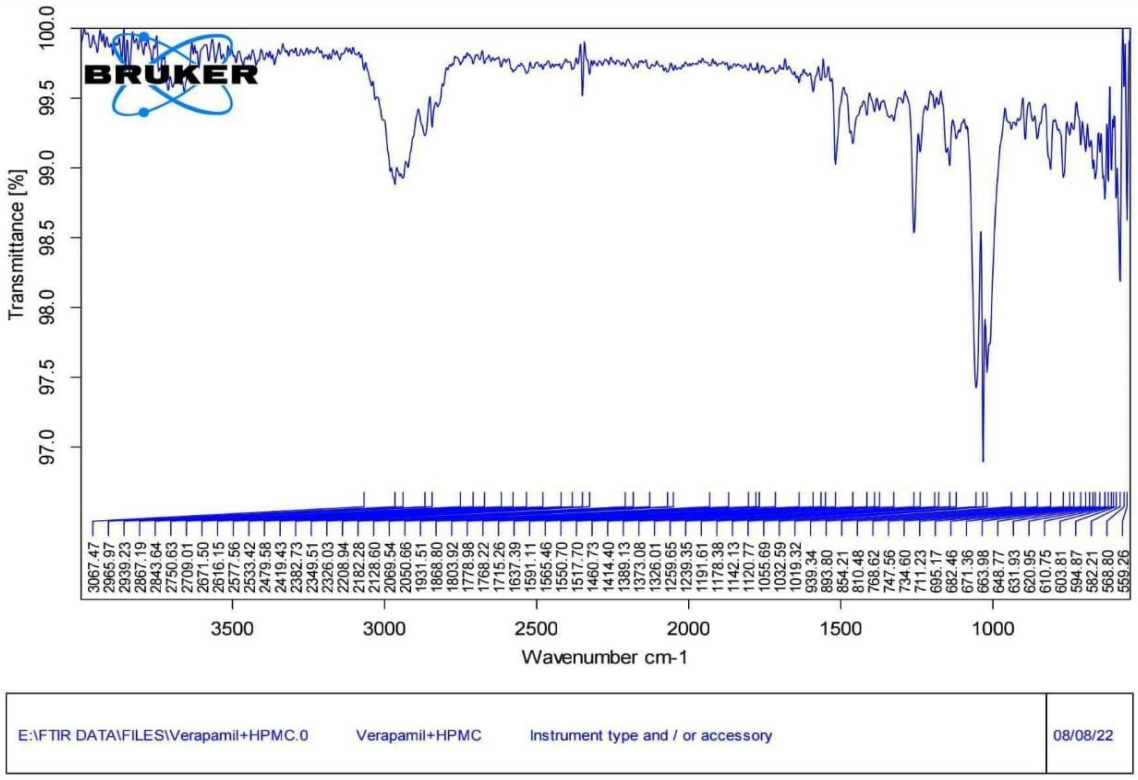

Figure 3: FTIR OF VERAPAMIL+HPMC

Particle size distribution: Cumulative retain pellets (%)

Table 3: Particle size distribution of pellets

Sieve number (#)	F1	F2	F3	F4	F5	F6	F7	F8	F9
14	1.2	1.5	2.5	2.0	1.3	2.3	3.5	3.3	3.0
16	35.3	36.0	31.0	30	32.0	31.0	45.0	45.2	45.5
18	64.5	65.5	74.5	65.8	67.8	66.6	73.5	70.2	69.0
20	86.5	89.5	91.5	80.5	95.8	81.6	83.5	82.2	85.2
25	100	100	100	100	100	100	100	100	100
Downs	0	0	0	0	0	0	0	0	0

Flow Properties: Flow properties of formulation from F1-F9. All the values are expressed as mean ±SD (n=3)

Table 4: Flow properties

Flow properties	F1	F2	F3	F4	F5	F6	F7	F8	F9
Bulk density(gm/ml)	0.69± 0.01	0.6± 0.02	0.67± 0.02	0.70± 0.03	0.69± 0.02	0.68± 0.03	0.73± 0.02	0.71± 0.01	0.67± 0.02
Tapped density(gm/ml)	0.74± 0.02	0.7± 0.04	0.73± 0.02	0.76± 0.03	0.74± 0.04	0.73± 0.05	0.76± 0.06	0.75± 0.08	0.72± 0.06
Hausner's ratio	1.07± 0.09	1.1± 0.08	1.08± 0.09	1.08± 0.07	1.07± 0.09	1.07± 0.08	1.04± 0.06	1.05± 0.07	1.07± 0.09
angle of repose	28.2± 0.8	28.± 0.78	28.0± 0.69	28.3± 0.90	27.6± 0.9	27.8± 0.82	28.1± 0.89	27.9± 0.75	28.6± 0.72

FRIABILITY

Table 5

F1	F2	F3	F4	F5	F6	F7	F8	F9
0.9± 0.1	0.76± 0.05	0.63± 0.13	1.23± 0.25	0.3±0.1	0.76± 0.15	0.6±0.1	0.73± 0.07	1.26± 0.11

Percentage Yield:

Table 6

F1	F2	F3	F4	F5	F6	F7	F8	F9
92.5	93.8	95.4	94.5	96.8	94.5	96.0	95.6	96.7

In-vitro Dissolution studies:

The formulations F1 to F3 were prepared by using different concentrations of HPMC E5 polymer. In-vitro drug release from pellets increased, because of the sustained release coating was not effective.

The release of drug was rapid as the Concentrations of lower viscous HPMC E5(~5cps) was insufficient to retard and slow release of the drug.

The formulations F4 to F6 were prepared by using different concentrations of HPMC 606 and ethyl cellulose polymer at different ratios (50:50, 60:40, 70:30). From the above results it was shown that F5 is effective in retarding release of the drug. The results of F5 fall in between USP specification. Sustained release coating was effective in F5 formulation.

The formulations F7 to F9 were prepared by using different concentrations of HPMC E15 polymer and ethyl cellulose polymer at different ratios (50:50, 60:40, 70:30). From the above formulations it was shown that release of the drug was very slow and not effective.

Table 7: Cumulative percentage drug release

S. No	Time (hours)	% Cumulative Drug release								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0	0
1	1	20±1.5	15±1.9	13±2.2	18±1.3	9±2.0	8.5±1.8	7±1.0	8±1.5	7.5±2.0
2	2	35±2.5	43±1.2	30±1.8	28±2.2	14±1.5	12±2.5	11.5±2.5	11±2.2	13±1.6
3	4	62±1.3	56±2.5	48±1.5	42±1.0	23±2.2	18±2.0	15±2.0	20±1.2	19±2.3
4	8	82±2.0	78±1.0	76±2.6	68±1.8	42±1.2	29±1.5	33±1.5	37±1.8	30±1.9
	24	96±1.8	94±2.3	95±2.0	96±1.5	94±2.5	87±1.0	82±1.0	75±2.0	89±2.1

CONCLUSION

The present study was carried out to formulate and prepare Verapamil Hydrochloride sustained release pellets using ethyl cellulose and HPMC based polymers. The percentage yield of F5 formulation was 97%.

The sustained release coating was effective for F5 formulation as it retards the drug effectively and releases the drug in controlled manner. The dissolution profile of F5 meets all the specifications according to dissolution data of USP.

REFERENCES

1. Amin, M. J., Pate, K. S., Patel, D. R., Patel, Z. P., & Bajag, J. V. (2021). Formulation and evaluation of sustained-release pellets of lornoxicam. *Int. J. Appl. Pharm*, *33*, 221-227.
2. Jawed, S. H., Muhammad, I. N., Qazi, F., Shoaib, M. H., Arshad, H. M., & Siddiqui, T. (2021). Development and Quality evaluation of sustained release pellets of eperisone HCl. *Pakistan Journal of Pharmaceutical Sciences*, *34*.
3. Manoharan, K., Bhaskaran, N. A., & Kumar, L. (2019). Pellets and techniques of pelletization. *Research Journal of Pharmacy and Technology*, *12*(12), 6157-6164.
4. Narender, K., Narayana Raju, P., & Sivakumar, R. (2018). Development and evaluation of bosentan pellets for prolonged drug release, *Indo American journal of Pharmaceutical Research*.
5. Rana, H. B., Gohel, M. C., Dholakia, M. S., Gandhi, T. R., Omri, A., & Thakkar, V. T. (2018). Development of sustained release pellets of galantamine HBr by extrusion spheronization technique incorporating risk based QbD approach. *Research journal of pharmacy and technology*, *11*(11), 4899-4910.
6. Bhalekar, M. R., Madgulkar, A. R., & Andure, S. S. (2017). Formulation and Evaluation of sustained release pellets of venlaflaxine hydrochloride. *Inernational Journal of Applied Research*, *3*(5), 793-799.
7. Manasa, V., Vanitha, K., Venkataswamy, M., Prabhakar, P., & Ramesh, A. (2016). Formulation and Evaluation of Aqueous Enteric Coated Delayed Release Omeprazole Pellets. *Research Journal of Pharmaceutical Dosage Forms and Technology*, *8*(1), 1-4.
8. Eskandari, S., Varshosaz, J., Akhavanfarid, G., & Hafizi, G. (2009). Formulation and in-vitro characterization of extended release pellets of indomethacin using powder-layering technique. *Research in Pharmaceutical Sciences*, *2*(2), 67-75.
9. Hussain, S. Z., Bhama, S., Selvi, R. S., & Srujan, L. (2011). Duloxetine hydrochloride delayed release pellets prepared by suspension layer method. *International Journal of Pharmaceutical Sciences and Research*, *2*(10), 2741-2745.

10. Amita, A. A., & Sachin S. (2015). Mali Pelletization technology: methods and applications -a review, *Research Journal of Pharmacy and Technology*, 8(2), 131.
11. Manasa, V., Vanitha, K., Venkataswamy, M., Prabhakar, P., & Ramesh, A. (2016). Formulation and Evaluation of Aqueous Enteric Coated Delayed Release Omeprazole Pellets. *Research Journal of Pharmaceutical Dosage Forms and Technology*, *8*(1), 1-4.
12. Mangesh, R. B., Ashwini, R. M., & Sumedha, S. A. (2017). Formulation and Evaluation of sustained release pellets of venlafaxine HCL, *IJAR*, 3(5), 793-799