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Research Article

Pharmacy for better health

Stable and Bio-Equivalent Formulation of Alginate Matrix-Based Verapamil Hydrochloride Extended-Release Tablets

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Abstract: Verapamil Hydrochloride is indicated to control blood pressure in individuals due to postural and nocturnal–diurnal variations in the biological clock. The once-daily administration of Verapamil Hydrochloride is handy for patients to comply with the dosing regimen prescribed. This research aims to develop stable, bio-equivalent, cost-effective, and commercially feasible Verapamil Hydrochloride extended-release tablets, 120 mg, 180 mg and 240 mg. Inorder to achieve this aim, our objective was to explore a simple aqueous granulation involving conventional excipients viz. Sodium Alginate, Povidone, Microcrystalline Cellulose and Magnesium Stearate. The drug to polymer ratio of 1:1.35 was found to be optimum. Every unit operation involved in the process was completely optimized to achieve reproducibility and to avoid drug release variation. The designed process was scaled-up from a batch size of 75,000 tablets to 750,000 tablets. During scalability, no difference is observed in the physico-chemical characteristics of the blend or tablets. The blend and content uniformity results were found to comply with USP requirements. The manufactured product was found stable in bottle and strip packs at accelerated stability conditions for 6 months. The maximum level of the highest unknown impurity observed was 0.1% and is well within the ICH Q3BR3 requirements. Hence based on stability study results, shelf-life storage of 24 months at controlled room temperature was prescribed for the product. The end product was found to be more cost-effective (3.2 to 6.4 Indian rupees) than the brand product available nationally (within India) priced at 4.7 to 9 Indian rupees, and the physico-chemical characteristics, drug release, and stability of the manufactured drug product were comparable to the brand product available in the USA market. The similarity factor 'f2' was found to be more than 75. In the Pharmacokinetic study, the test to brand product ratio at 90% confidence interval was within 80.00-125.00%, exhibiting the developed product's bio-equivalence with the brand product. Novelty in this research is in the comprehensiveness of work done to demonstrate stability, bio-equivalence, cost-effectiveness and commercial ability aspects which were not reported elsewhere in the already published research work on Verapamil extended release tablets.

Keywords: extended release matrix tablet, pharmacokinetics and pharmaco-economics.

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1. INTRODUCTION

Verapamil Hydrochloride was approved for medical use in 1981[1]. The drug is a calcium channel blocker for the treatment of high blood pressure[2], angina pectoris[3], atrial fibrillation[4], supraventricular tachycardia[5], migraine[6], cluster headaches[7]. Drug is more effective than digoxin[8] in Cardiac arrhythmia[9]. The drug is used by intra-arterial route for cerebral spasm[10-11]. Topicallythe drug treats Plantar fibromatosis[12-14], Peyronie's disease[15-16], Dupuytren's disease.[17-18] In Veterinary Science, following surgery in rabbits the drug is used to prevent intra-abdominal adhesions[19-21]. In cell biology[22-24] the drug is used to study the P-Glycoprotein[25-28] and ABC transport protein functions[29-32] due to the inhibition of drug efflux pump proteins[33-35]. Verapamil Hydrochloride is a commonly prescribed medicine in India of about 20 million doses[36-37] and in the United States about 4 million doses per year.[38-39] Verapamil Hydrochloride is available as a sustained release tablet and injectables in India and USA. In India, the average unit price of sustained release tablet manufactured by Abbott under the brand name CALAPTIN® supplied in strip packing is 4.66 Indian rupees per tablet of 120 mg strength and 9.17 Indian rupees per tablet of 240 mg strength.[40] In USA, the average unit price of extended-release tablet manufactured by Pfizer under the brand name CALAN SR® supplied in bottle packing is 6.55 US dollars per tablet of 120 mg strength, 8.61 US dollars per tablet of 180 mg strength and 9.83 US dollars per tablet of 240 mg strength.[41] Aim of the present research is to develop a stable, bioequivalent, cost-effective, commercially feasible formulation of Verapamil Hydrochloride extended-release tablets, of strength 120 mg, 180 mg and 240 mg that exhibits comparative physico-chemical characteristics and drug release behavior similar to the international brand, CALAN SR® and cost-effective as compared to national brand, CALAPTIN®. To fulfill the aim, the objective of the research is in coming up with a simple composition involving conventional excipients and with a straightforward process that is reproducible from lab-scale to commercial scale in giving a quality product that shows comparable physico-chemical characteristics and drug release behavior as compared to the brand product, and at the same time, the developed product must be cost-effective than the market counterparts. Before venturing into formulation trials, a literature and patent review was done on the existing design of extended-release tablets of Verapamil Hydrochloride. As evident from Patent and Literature review there are various approaches in designing the extended release tablets of Verapamil Hydrochloride involving Carbopol 971P[42], HPMC K15M CR[43], Xanthan gum and Locust bean gum[44], Sodium Alginate[45], HPMC K100M and Sodium Alginate[46], HPMC K100LV[47], Ethylhydroxyethyl Cellulose and Tamarind Polyose[48], Polyethylene Oxide N80, Ethyl Cellulose 7 cps and HPMC 50 cps[49], Carbopol 974P, Eudragit NE30D and Ethyl Cellulose 7 cps[50], Eudragit RLPO[51], Guar Gum[52], HPMC K15MCR, Mannitol (Osmogen) and Ethyl Cellulose 7 cps in coating[53], Pectin[54], Glyceryl Monostearate[55], Xanthan gum and HPMC K15MCR[56], HPMC K100MCR and Carboxymethyl Cellulose[57], Tragacanth and Acacia[58], HPMC K100LV and Eudragit RS 30[59], Carnauba wax and Polyethylene Glycol 6000[60], Potassium Chloride and Cellulose Acetate[61], HPMC K100MCR and Xanthan gum[62], HPMC K100MCR and Sodium Carboxymethyl Cellulose[63], HPMC E15 and Carbopol 974P[64], Hydroxyethyl Cellulose[65], Hydrogenated Cottonseed Oil and Carbopol 934P[66], Mannitol, Polyethylene Oxide, Cellulose Acetate and Hydroxypropyl Cellulose[67], Sodium Alginate and HPMC E4M[68], Hypromellose Phthalate 55 and Eudragit NE 30D[69], Eudragit NE30D and Eudragit L30D55[70], Ethyl Cellulose and HPMC[71], Sodium Alginate[72], Sodium Alginate and Eudragit RS[73], Polyethylene (Epolene C-10) and Ethyl Cellulose 100 cps[74]. In all the mentioned literature and patent publications, the completeness of research in-terms of stability, bio-equivalence, cost-effectiveness, and commercial feasibility is missing in entirety. However, based on the literature and patent review, the efforts of various researchers to design the extended-release tablets of Verapamil Hydrochloride are evident and able to make the pros and cons of every approach. Once daily dosing of Verapamil HCl is advantageous from patient compliance viewpoint and for effective control of blood pressure fluctuation. The brand product available nationally and internationally is a hydrogel matrix based extended-release tablet in which alginate serves as a polymer to sustain the drug release. For such hydrogel based matrix systems, the mechanism of drug release is by a combination of diffusion and erosion. The drug delivery system design in most of the research work (literature / patent) is a matrix system with erosion or diffusion control. There are reported references on systems that had both erosion and diffusion mechanisms too. Few researchers have attempted a controlled osmotic system to modulate drug release. In the current research, a matrix-based drug delivery system shall be designed with minimal excipients, which are cost-effective and commonly available. By doing so, the manufactured product will be cost-effective among the market counterparts. During the composition and process design, care shall be taken so that the manufacturing process is robust enough to result in a quality end product without any device failure and that the drug release characteristics of the designed product is comparable to the brand product. Being a part of a Pharmaceutical company involved in R&D and commercialization of quality drug products, I hope this research article will kindle interest in both academia and industry circles alike to bring research articles that not only seem attractive from a research perspective but also has a good commercial angle so that the designed and manufactured end-product reaches the patient at a cost-effective price.

2. MATERIALS AND METHODS

2.1 Materials

Verapamil HCl API (Active Pharmaceutical Ingredient) was sourced from Aurore Lifesciences. Excipients used were of compendial grade. Solvents, salts & reagents used were of analytical grade.

2.2 Methods

Verapamil HCl and its products are official in USP, hence adopted the monograph methods for assay, content uniformity, blend uniformity, water by Karl Fischer, loss on drying, related substances and dissolution analysis.[75-76] Regarding the determination of bulk density, tapped density, compressibility index, Hausner ratio, angle of repose, particle size distribution, and friability test referred to the procedure prescribed.[77] Viscosity was determined based on the procedure.[78]

3. RESULTS & DISCUSSION

3.1 API Characterization

Bulk density, tapped density, particle size distribution, compressibility and flow of API, Verapamil HCl are presented

in Table.1. Based on the Hausner ratio and Compressibility index it is evident that API exhibits poor flow and compressibility. Hence the direct blending and compression process was not feasible and need to explore alternative processes like granulation to improve on the blend flow and compressibility.

Table.1 Verapamil HCl API characterization	
Bulk density, g / mL	0.28
Tapped density, g / mL	0.53
Compressibility index, %	47
Hausner ratio	1.89
Angle of repose,°	40
Particle size distribution (d90 in microns)	86

3.2 Brand Product Characterization

Verapamil HCl brand product's excipients, color, form, shape, dimension, weight, thickness, hardness, viscosity, % dissolution etc are presented in Table.2. The disintegration time was not tested, since the tablets are extended release coated. Based on brand product characterization data, targets were set for the development of the test product. Brand product was physico-chemically characterized, and reverse engineering tested to qualify and quantify excipients viz. Sodium Alginate[79], Povidone[80], Microcrystalline Cellulose[81] and Magnesium Stearate[82]. Based on these studies, the composition was designed for the test product. The finalized composition, process, stability, drug release and unit pricing are shown in Table.3 to Table 6.

Table.2 Brand product characterization				
Particulars		**120 mg**	**180 mg**	**240 mg**
Excipients		Alginate, Carnauba wax, HPMC, Magnesium Stearate, Talc, PEG, Microcrystalline Cellulose, Povidone, Titanium dioxide, D&C Yellow #10+FD&C Blue#2 lake (240 mg), Iron oxide (120 mg & 180 mg).		
Color		Violet	Pink	Green
Form		Coated tablet	Coated tablet	Coated tablet
Shape		Oval	Oval	Caplet
Dimension, mm		11.13 X 6.43	15.55 X 7.82	18.57 X 6.48
Weight, mg		370±3	555±2	740±4
Thickness, mm		6.50±0.03	5.89±0.03	6.22±0.04
Hardness, Kp		17±4	11±4	21±4
Viscosity, cps		56,000±1010	82,500±900	110,000±1100
Dissolution	**Time, hr**	**Mean % dissolved and %RSD**		
	1	9±4	11±4	10±5
	2	22±3	18±3	19±4
	3.5	38±3	42±2	40±4
	5	60±3	64±2	62±2
	8	97±2	99±3	97±2

3.3 Trial Preamble

The extensive literature and patent review as well as the brand product characterization study made it possible for us to not only reduce the number of development trials to arrive for the final composition and process but also to match the drug release with the brand product by in-vitro and in-vivo[83].

3.4 Composition – Qualitative Functionalities

The composition in Table.3 was defined as intragranular and extragranular parts for easy differentiation of function and related unit operation lines involved in the manufacturing.[84] This usually occurs in any granulation process other than direct blending and compression. Functionally, Sodium Alginate is a drug release controlling matrix agent and provides the necessary acidic pH microenvironment for the drug to solubilize in the intestinal alkaline pH[85] since Verapamil Hydrochloride exhibits acid-dependent solubility[86]. Povidone is a binder to provide the necessary adhesion attribute for the blend to get compressed into tablets[87]. Microcrystalline Cellulose is used as a diluent/filler in the composition and added in both intra and extragranular portions for better flow and compressibility[88]. Magnesium Stearate is used as a lubricant to enable tablet compression using punch toolings without picking, sticking, and striation issues[89]. The readymade Opadry coating materials of Polyvinyl acetate (PVA) grade were utilized. The specific advantage of the use of PVA grade is the reduction in total coating time due to faster coating build-up which is due to high solid content coating dispersion of 20% w/w solids[90]. The shade or color of the Opadry coating material was kept similar to the brand product.

Table.3 Composition, Process and In-process checks

Ingredients	mg per tablet			Process Remarks
Intragranular portion				Security screening: #16 mesh Granulation in HSMG
Verapamil HCl	240	180	120	@ Impeller low rpm: 5 min dry mix.
Sodium Alginate, LV	325	243.75	162.5	@ Impeller & chopper fast rpm.
Povidone, 30 cps	47	35.25	23.5	3 min granulating fluid addition. 3 min kneading
Microcrystalline Cellulose, 101	30	22.5	15	Drying in Fluid Bed Dryer Inlet. 60 ±5°C; Air flap. 60%; % LOD. NMT 5%.
Purified water (mL) [Granulating fluid]	190	142.5	95	Milling in Comminuting Mill 1.5 mm screen, Knife forward, Medium speed.
Extragranular portion				Security screening: #16 mesh for MCC, 102; #40 mesh for MgS. Blending in DCB @15 rpm: Prelubrication: 10 min; Lubrication: 4 min. BD,g/mL. 0.43; TD,g/mL. 0.61; CI, %. 30; HR. 1.42.
Microcrystalline Cellulose, 102	77.5	58.625	38.75	
Magnesium Stearate, Veg grade	2.5	1.875	1.25	

Sieve#	20	40	60	80	100	pan
%retain	2	31	17	9	5	36

				Mean value	240 mg	180 mg	120 mg
Core tablet weight, mg	722.0	542.0	361.0	Weight,mg	719±3	541±2	360±3
				Thickness,mm	6.1±0.03	5.81±0.04	6.41±0.02
				Hardness,Kp	16±3	11±3	15±2
				% Friability	0.11	0.09	0.12
Film Coating							
Opadry II Green 85F18422	18	-	-	Inlet. 65 ±5°C; Bed. 45 ±5°C; Spray rate. 15-20 g / min; Pan speed. 12 rpm; Atomization. 2 bar; Gun-bed distance. 12 cm; Nozzle. 1.2 mm; Solids. 20%.			
Opadry II Pink 85F18422	-	13.5	-				
Opadry II Violet 85F18422	-	-	9				

Kp: Kilo pond; DCB: Double Cone Blender; BD: Bulk density; TD: Tapped density; CI: Carr's index; HR: Hausner ratio; MCC: Microcrystalline Cellulose; MgS: Magnesium Stearate; HPMC: Hypromellose; PEG: Polyethylene Glycol; LV: Low viscosity; LOD: Loss on drying; cps: Centipoises; rpm: revolutions per minute; NMT: Not more than; HSMG: High shear mixer granulator; Impeller slow rpm: 150; Impeller fast rpm: 200; Chopper slow rpm: 1500; Chopper fast rpm: 2000;

3.5 Process – Unit Operation Finer Details & Optimization

As evident from the 3rd column entitled 'Process Remarks' in Table.3, the manufacturing process starts with security screening and is for de-lumping and also to remove any extraneous foreign material[91]. The screened ingredients were loaded into High Shear Mixer Granulator and dry mixed for 5 minutes. The dry mix time of 5 min was finalized based on the blend uniformity data in 6 different locations at 4 min, 5 min, and 6 min. It was found that 5 min was sufficient for dry mixing. Since the process is an aqueous granulation, purified water is used as a granulating fluid[92]. For granulation, the amount of Purified Water addition (fluid uptake) was optimized[93] at 29.5% w/w to the amount of intragranular ingredients based on the previous studies done at 24.5%, 29.5% and 34.5% w/w. The purified water addition time for granulation was fixed at 3 min within which complete Water addition was done, and the subsequent kneading for 3 min was finalized based on the monitored amperage reading and double-confirmed by manually testing the granular material consistency[94]. The drying was done in fluid bed dryer and limit for the drying process is based on the dry mix's % Loss on drying value and also based on the theoretical equilibrium moisture content of the intragranular ingredients[95] and is 5%w/w; hence the same was fixed as %Loss on drying limit for the dried granules. The milling process influences the granules-to-fines ratio of the blend and affects the blending flow and compressibility[96]. Hence milling study trials were done with 1.0 mm, 1.5 mm and 2.0 mm screen apertures in the Comminuting mill operated at medium speed knife forward configuration. 1.5 mm screen aperture was finalized for milling process based on blend uniformity by %RSD in 'between' and 'within location'; blend flow measurement by Angle repose and Hausner ratio and blend compressibility measurement by Carr's index. Care was exercised during the extragranular addition of Microcrystalline Cellulose and Magnesium Stearate to the milled intragranular part[97]. Microcrystalline Cellulose exhibits plastic deformation and mixing of Microcrystalline Cellulose and Magnesium Stearate will affect compressibility and precipitate tablet defects like capping and lamination[98]. Hence, the extragranular ingredients were added individually and blended with the intragranular part. Accordingly, the blending time study was done separately for pre lubrication blending time involving the addition of Microcrystalline Cellulose to the intragranular part and, subsequently, the lubrication blending time involving the addition of Magnesium Stearate to the pre lubricated blend[99]. Concerning blending time optimization[100] in pre lubrication and lubrication stages, the 'rpm' of the blender is fixed at 15, and blending was done for 5, 10 and 15 minutes in prelubrication stage and 3, 4 and 5 minutes in the lubrication stage. Blend uniformity samples were withdrawn at 10 different locations in the blender at all mentioned time-points in both stages. Based on the 'blend assay uniformity', a blending time of 10 min was finalized for the prelubrication stage and 4 min for the lubrication stage. The final blend thus obtained by dose-proportional approach was compressed into tablets using high-speed tablet press enabled with tooling' of 11.1 X 6.4 mm Oval shaped, 15.6 X 7.8 mm Oval shaped and 18.6 X 6.5 mm Caplet shaped punch toolings to compress 120 mg, 180 mg and 240 mg strengths respectively.

As part of the compression process, speed variation and hardness variation were studied to study the influence of turret speed variation on content uniformity and tablet hardness variation on dissolution profile[101]. Speed variation study was done at 15, 30 and 45 rpm, and at each speed, samples were collected and evaluated for turret speed influence on weight variation, hardness variation and content uniformity. It was observed that uniformity of weight was maintained within ± 6 mg, hardness uniformity was maintained within ± 3 Kp and the 'L1' value in content uniformity or uniformity of dosage units testing of 10 units per each speed was well within compendial requirements of 15. Hence the turret speed was fixed at 15-45 rpm with the target turret speed of 30 rpm. In the hardness variation study, the tablets were compressed at 10, 15 & 20 Kp and at each hardness level, samples were collected and evaluated for hardness influence on friability and % dissolution. It was observed that % friability was well within 1% w/w and the mean % dissolved across the hardness range studied was comparable to the brand product. Hence the hardness range during compression was fixed at 10-20 Kp with a target hardness level of 15 Kp. The core tablets were then film-coated in a fully perforated coating pan upto 3 different coating build-ups viz. 1%, 2.5% and 4% w/w. The tablets were then tested for dissolution to check the influence of the % coating build-up on the drug release. It was observed that there is no significant difference in 'mean % dissolved' across the coating build-up range studied and the dissolution numbers are comparable to the brand product. This observation is expected since film-coating is for aesthetic sense and will not affect/modulate the drug release from the core matrix tablet. Hence the film-coating build-up range was fixed between 1-4% w/w with target coating build-up of 2.5%w/w. Disintegration time was not evaluated in the compression and coating stage since the formulation is a controlled release matrix tablet[102]. The coated tablets thus obtained were packed in high-density polyethylene bottles equipped with child-resistant closure using CVC packing line and also in strip pack using 6 channel strip packing machine. The packing integrity was checked by performing leak testing under a vacuum every 15 min.

3.6 Stability Evaluation of Intended Packs

The bottle-packed and strip packed tablets were subjected to accelerated storage conditions of 40°C / 75% RH for 6 months[103] and evaluated for assay, related substances – highest unknown impurity due to degradation, water by kf and dissolution[104].

Table.4 Stability evaluation

Particulars	mg / tablet			Results				
Coated tablet weight, mg (Initial / T_o time point)	740.0	555.5	370.0	**Tests**		**240 mg**	**180 mg**	**120 mg**
				Weight,mg		737	555	369
				Assay,%		99.4	99.1	98.9
				HUKI,%		0.03	0.01	0.04
				Water by Kf,%		4.32	4.19	4.38
				Viscosity, cps		112000	87000	59000
				Time (hr) Vs % Mean Dissolution	1	8±4	11±3	10±5
					2	22±3	18±3	25±4
					3.5	37±3	42±3	38±3
					5	65±3	64±3	63±3
					8	99±3	99±3	98±3

Coated tablet in bottle and strip pack at 40°C/75%RH for 6 months	**Tests**		**240 mg**		**180 mg**		**120 mg**	
	Pack		Bottle	Strip	Bottle	Strip	Bottle	Strip
	Assay,%		97.9	98.1	98	98.3	97.1	97.9
	HUKI,%		0.09	0.06	0.08	0.05	0.10	0.06
	Water by Kf		4.81	4.63	4.79	4.59	4.72	4.54
	Time (hr) Vs % Mean Dissolution	1	13±4	10±3	12±4	12±3	12±4	13±4
		2	26±3	20±3	21±4	17±3	28±4	22±3
		3.5	41±3	36±3	44±3	45±3	37±4	36±3
		5	69±3	66±3	67±3	67±3	68±3	64±3
		8	100±3	98±3	100±3	99±3	100±3	99±3

Note. h: hour; KF: Karl Fischer; HUKI: Highest Unknown Impurity; LOD: Loss on drying; cps: Centipoises; rpm: revolutions per minute; NMT: Not more than; %RSD: % Relative Standard Deviation.

Stability data, as evident from table. 4 above showed a perfect mass balance between the initial and 6th month where the assay, related substances and water by kf numbers are in equilibrium / in sync as per Arrhenius stability isotherm[105]. Moreover, the maximum observed % degradation i.e. the highest unknown impurity, is 0.1% and is well within the ICH Q3BR3 requirements. Hence based on the stability study results, shelf-life of 24 months at controlled room temperature storage was prescribed for the product in bottle and strip pack.

3.7 Pharmacokinetic Study

Pharmacokinetic study was conducted in 14 healthy, adult male human subjects. A randomized, two treatments, two sequences, two periods, two ways cross over study was done in which 240 mg strength of test formulation was compared with brand product. Only a ""FASTING" study was performed. Subjects were housed in a clinical facility to ensure overnight fasting of 10 hours. Subjects remained in the facility till 24 hours' post-dose and again reported

ambulatory blood samples for 36 and 48 hours in each period. Subjects were dosed in sitting positions using 240mL of water and remained seated for the first 4 hours. No fluid was allowed 1 hour before & after dosing. The washout period between the two periods was seven days. Upon completion of the study, the physical examination and clinical laboratory measurements were repeated. Sampling was done at predetermined time intervals of 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 20, 24, 36, 48 hours. The pharmacokinetic and statistical analysis was performed using WinNonlin® version 5.0 (Pharsight Corporation, USA). Pharmacokinetic analysis was performed employing a model-independent method[106]. The maximum concentration (C_{max}) of Verapamil and its major metabolite Norverapamil and the corresponding peak times (T_{max}) were determined by estimating the individual drug plasma concentration-time profiles. The elimination rate constant (k_{el}) was obtained from the least-square fitted terminal log-linear portion of the plasma concentration-time profile. The elimination half-life ($T_{1/2}$) was calculated as 0.693/ k_{el}. The linear trapezoidal rule calculated the area under the curve to the last measurable concentration (AUC_{0-t}). The area under the curve extrapolated to infinity as (AUC_{0-t} + Ct/ k_{el}, where Ct is the last measurable concentration. For the purpose of statistical bioequivalence analysis AUC_{0-t}, $AUC_{0-\infty}$ and Cmax were considered as primary variables[107]. Study protocol (VER-21-008-01) was approved by an Independent Ethics Committee - The Ethical Jury, Chennai (Ref. No. LEC/2021/023). The studies were conducted in compliance with the ethical principles of the Declaration of Helsinki, the International Conference on Harmonization's Good Clinical Practices guidelines, and the Indian Council of Medical Research for Biomedical Research on Human Subjects guidelines and Good Clinical Practices for Clinical Research in India. Healthy, willing, volunteers of age between 18 and 50 years were selected based on laboratory evaluations during screening, medical history, clinical examination, X-ray, ECG recordings, urine screen for drugs of abuse, and alcohol breath test. Informed consent was obtained from the subjects after explaining the nature and purpose of the study[108]. There is no safety or toxicity concern involved because the drug 'Verapamil Hydrochloride" has been available in the market since 1981. Also, the committee reviewed the in-vitro drug release profile of both the test and brand product and were satisfied with the least or no risk on the possibility of dose-dumping in volunteers. The similarity factor 'f2' was more than 75 in the brand and test dissolution profile comparison.

Table.5 Pharmacokinetics

Pharmacokinetics Verapamil (Norverapamil)	Ln AUC_{0-t} (ng.h/mL)	Ln AUC_{inf} (ng.h/mL)	Ln C_{max} (ng/mL)	t_{max} (h)	Half-life (h)
Brand product, 240 mg	7.1 (7.4)	7 (7)	4.8 (4.7)	5.9 (5.9)	8.4 (8.4)
Test product, 240 mg	7.1 (7.4)	7.1 (7.5)	4.8 (4.6)	6.5 (6.5)	7.9 (7.9)
Ratio of LSM, %	103 (105)	104 (106)	97 (92)	-	-
90% Confidence Interval, %	87-121 (89-123)	88-122 (90-124)	80-118 (81-109)	-	-

Note. LSM: Least square mean; US: United States of America; ng: nanogram; h: hour; Ln: Natural logarithm; AUC: Area under curve.

In the bioequivalence study, the time-based blood profile of both 'Verapamil' and its primary metabolite 'Nor-Verapamil' was evaluated and compared between the test and brand product as mentioned in the above Table.5. The study findings showed the bioequivalence of the test product to the brand product i.e. the test to brand product ratio at 90% confidence interval with respect to C_{max}, AUC_{0-t} and AUC_{0-Inf} was within 80.00-125.00% exhibiting the bio-equivalence of the developed product with the brand product.

3.8 *Scaling-Up and Commercial Feasibility*

The purpose is to evaluate the feasibility of scaling-up from lab scale batch size of 75000 tablets to a commercial-scale batch size of 750,000 tablets. Between the Lab Scale and commercial scale, especially for processes viz. milling, compression and packing the equipment used is of a standard capacity and is common for both lab scale and commercial scale batches; hence no optimization / validation is required. However, for the process involving granulation in high shear mixer granulator, fluid bed dryer, double cone blender, and tablet coater the capacity used for Lab scale is 100 L, 125 L, 150 L and 48" respectively and for commercial scale the capacity of corresponding equipment used are 600 L, 800 L, 750 L and multiple sub-lots of coating in 48". Since the equipment design is the same for granulation and the % occupancy of intragranular ingredients in equipment is comparable, the process parameters for dry mix, water addition during granulation, and subsequent kneading were kept the same. The amperage observed during the granulation end-point was comparable. In the case of drying, the parameters are kept the same except % flap opening for fluidization of granules. The total drying time was comparable across the batch size. For blending, the blender RPM was kept constant at 15 RPM. Since blend uniformity study was done in lab scale, the appropriateness of the blending time was validated and holds good in a commercial scale with 15 min for pre lubrication and 4 min for lubrication. The equipment used was a 48" fully perforated coating pan in the coating process. The process parameters that varied between the lab scale and commercial scale were atomization pressure, spray rate, gun to bed distance and RPM of coating pan. In the commercial scale batch, the atomization pressure was reduced one-fold, spray rate per gun was increased by 2 folds, gun to bed distance was reduced proportional to the material load in pan, RPM of coating pan was increased 2 folds. The rest of the coating parameter settings remained the same. The total coating time to achieve the target coating build-up in the commercial batch was comparable to the lab scale batch. Since the product is an extended-release tablet for once-daily use, the dose dumping and device failure risk was evaluated for the manufactured product by performing an alcohol dose-dumping study[109] and divisibility study[110] for 240 mg strength of both the brand and test product. The dissolution profile of the test product was comparable to the brand product in both alcohol dose dumping study and in divisibility study showing the quality of product manufactured in a commercial scale.

3.9 Pharmacoeconomics

The cost of the manufactured product was calculated[111] using software, Tally ERP 9 module. The costing involves, Material cost - cost of drugs and other pharmaceutical aids used, including, overages and process loss; Conversion cost worked out following procedures of costing and fixed; Cost of packing material of formulation including, process loss; Packing charges worked out in accordance procedures of costing; Maximum Allowable Post-manufacturing Expenses includes all costs incurred by the manufacturer from ex-factory to retailing stage and includes, margin for manufacturer and trade margin and was not more than one hundred per cent for indigenously manufactured Scheduled formulation and this varies for the export market with significant costing in licensing, export fee, logistics etc; Excise duty cost; Additionally for export, landing cost form the basis for fixing price along with margin to cover selling and distribution expenses and importer's profit not exceeding fifty per cent of landed cost.

Table.6 Pharmacoeconomics

Cost of developed Verapamil HCl ER Tablet	120 mg	180 mg	240 mg
Unit Price Indian Market in ₹	3.2	4.8	6.4
Unit Price US Market in $	2.1	3.2	4.3

With the said calculations, from Table.6 it is evident that the manufactured product was found to be more cost-effective (3.2 to 6.4 Indian rupees) than the brand product available nationally (within India) priced at 4.7 to 9 Indian rupees and also when exported and distributed in a country like USA, the manufactured product is offered at 2.1 to 4.3 US dollars than the US Market brand priced between 6.55 to 9.83 US dollars. From the Pharmacoeconomics perspective[112], the time managed in the commercial manufacturing of Verapamil HCl extended-release tablets was also accounted. The total time taken for a commercial batch process of granulation, drying, milling, and blending is 6 hours. This was possible due to optimized operating ranges for each unit operation. Good blend flow and compressibility are due to granules to fines ratio of 60:40, Carr's index of 30 and Hausner ratio of 1.4. This enabled us to complete the compression process of a commercial batch in 6 hours! In the coating process, use of Opadry II material with the dispersion of 20% solid content made the difference in completing a commercial batch in 6 hours! With the parallel operation of bottle and strip packing lines, the total time to complete the commercial packing operation is 6 hours! Hence, with the finalized composition and process, a commercial batch can be made in 24 hours or in 3 shifts, which is an indication of effective management of resources, minimal idle time and wastages leading to cost-effectiveness.

4. CONCLUSION

Alginate based Verapamil HCl extended-release matrix tablet was successfully formulated by dose-proportional design. The drug-to-polymer ratio of 1:1.35 was found optimum to achieve comparable drug release to the brand product. The finalized manufacturing process assured content uniformity and drug release control. The drug product was stable at accelerated storage conditions of 40°C / 75% RH for 6 months, thus ensuring 24 months' shelf life. The end product was found to be more cost-effective than the national brand product (available within India) and the physicochemical characteristics, drug release (in-vitro dissolution and in-vivo bio-equivalence), and stability of the manufactured product were comparable as well as cost-effective than the international brand product (available in USA). The commercial feasibility of the formulation was successfully evaluated by scaling up from batch size of 75000 tablets to 750,000 tablets. Hence in this research, Verapamil Hydrochloride extended-release tablets, 120 mg, 180 mg and 240 mg was successfully developed with a simple alginate based matrix design and the manufactured product was found to be stable, bio-equivalent, cost-effective and commercially feasible, which will benefit not only the patient population but also the company engaged in the pharmaceutical operation.

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6. AUTHOR'S CONTRIBUTION STATEMENT

All the authors have equally contributed in one way or the other in bringing up this research article. Since this laborious and manpower-intensive research work involved conceptualization, literature collection, brand product evaluation, composition, and process design, analysis, bio-equivalence, costing, scalability, compilation, and review.

7. CONFLICT OF INTEREST

Conflict of interest declared none.

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