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Design and development of Multiple-Unit, Extended release drug delivery system of Verapamil HCL by Pelletization Technique

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Abstract

Today, the scenario of pharmaceutical drug delivery is changing from conventional dosage form to novel drug delivery system with main objective of patient compliance. The main objective of the present study was to develop a multiple-unit, extended drug delivery system for prolong drug release through out the day. Verapamil HCL is an antihypertensive drug, having pH dependent solubility and is being used successfully for the treatment of hypertension and other cardiovascular diseases; hence it was used as a model drug. Weakly basic drugs or salts thereof demonstrate pH-dependent solubility. The resulting release from the conventional matrix system decreases with increasing pH of the gastrointestinal tract. Present study involves development of a multiparticulate drug delivery system to overcome this problem and to achieve pH-independent drug release. In this research work Organic acids such as fumaric & malic acid were added to the drug–polymer system were added as a pH-adjuster inside the pellet core for the maintenance of constant acidic micro-environment inside the core of dosage form. Pelletization technique was selected for the formulation of verapamil HCL to reduce the inter individual variations in plasma levels. PH-independent drug release was achieved from pellets consisting of organic acid in their core when coated with selected pH-independent coating polymers like ethylcellucose, hydroxypropylmethyl cellulose and Eudragit. Organic acids are pH-adjuster at higher pH. Therefore, they are able to compensate the poor solubility of weakly basic drugs at high pH. This approach was successful when using organic acids that demonstrated creating an acidic

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***Key words*:**

Pellets, Pelletization technique, Verapamil HCL, pH-independent polymers, antihypertensive drug.

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Introduction

Modified release formulation technologies offer an effective means to optimize the bioavailability and

resulting blood concentration time profile of drugs[1]. Modified release dosage forms are preparations where the rate and/or site of drug release of the active substances(s) are different from that of a conventional release dosage form administered by the same route. The concept of the multi unit dosage form was introduced in the early 1950s. These solid oral dosage forms consist of a multiplicity of small discrete particulates, which include mini tablets, pellets and granules[2]. These systems provide flexibility during formulation development and gives therapeutic benefits to patients. Pellets offer advantages as they constitute multi unit dosage forms, studies have indicated that they are rapidly and evenly dispersed in the gastrointestinal tract upon oral administration, thus maximizing drug absorption and reducing inter- and intra-subject variability due to differences in gastric emptying rates[3]. Pellets can be filled into hard gelatin capsules or compressed into tablets, which rapidly disintegrate into multiple units. Multiple units include Pellets, Granules, Microcapsules, and Beads etc. There are certain challenges associated with the formulation of drugs with pH-dependent solubility affecting the release from dosage and hence absorption. It is imperative that a controlled release oral formulation should have uniform release pattern at different sites of GIT over the period of dosing. Weakly basic drugs or salts thereof demonstrate pH-dependent solubility. The resulting release from matrix system decreases with increasing pH-milieu of the gastrointestinal tract. Some study was carried out & some delivery systems were developed to overcome this problem and to achieve pH-independent drug release. Two different approaches to solve the problem of pH-dependent release of weakly basic drugs are demonstrated in some literatures. The first one is based on the addition of an enteric polymer (hydroxypropyl methylcellulose acetate succinate), the second one is the addition of organic acids such as fumaric, succinic or adipic acid to the drug–polymer system. The first approach almost failed to achieve pH-independent drug release, whereas the addition of organic acids to the matrix forms was found to maintain low pH values within the drug delivery system like tablets, pellets, etc. The word *"pellet"* has been used to describe a variety of systematically produced, geometrically defined agglomerates, obtained from diverse starting materials utilizing different processing conditions. *"Pelletization"* is an agglomeration process that converts fine powders or granules into small, free flowing, spherical or semi spherical units, referred to as pellets[4]. Pellets uniformly distribute through out the gastrointestinal tract, they invariably maximize drug absorption, reduce peak plasma fluctuations and minimize potential side effects without appreciably lowering bioavailability.

Materials & Methods

The following materials were used in this study. All the materials used were supplied by the manufacturers without further modification after ascertaining that they confirmed to the required standards. Verapamil Hydrochloride (Nicholas Piramal Ltd. Mumbai), Microcrystalline cellulose(FMC Biopolymers, Ireland), Fumaric Acid(Merck, Germany), PVP-K 30(ISP Technology), Triethyle citrate (Jungbun Zlaver), PEG-6000(Vasudha chemicals Ltd.), EC-45 cps, EC-20 cps(Colorcon, Mumbai), Eudragit NE30D, Eudragit-RS100, Eudragit-RS100(Degussa Pharma (Rohm), Mumbai), Talc(Signet, USA)

1. Preparation of core pellets:

The core verapamil pellets were prepared by extrusion spheronization technique. Mixed the weighed quantity of Verapamil HCL, MCC (Avicel pH 101) and *organic acid* in granulator (Rotating Mixer Granulator, Jaguar) for dry mixing (5 min.) before addition of binder solution. Prepared a binder solution of PVP-K30 in water and added in powder

mixture in specified time continuously (3 min.). A wet mass was removed from granulator after sufficient kneeding (30 sec. at high speed and 30 sec. at low speed).

A) Extrusion-Spheronization:

Wet mass was passed from suitable screen (0.8 mm) of extruder (Fuji Paudal, Japan). Extrudes was spheronized in Spheronizer for a specific time (5-7 min.) and dried the product till LOD was NMT 2% (Separated the required fraction (0.84 to 1.50 mm) by sifting the pellets obtained after drying of pellets). The over and under size pellets were crushed and reused in the next lot of extrusion.

Constant parameters for extrusion:

a) Die-roller size (pore diameter) - 0.8 mm
b) Speed of Die-roller - 40 rpm

Constant parameters for spheronization:

a) Friction plate type - Crosshatch pattern
b) Groove size - 1 mm
c) Spheronizing speed - 1200 rpm
d) Spheronization time - 7 minutes
e) Feed size - 120 gm

B) Coatings:

Small quantity of prepared core pellets were seal coated in conventional pan coater and then functional coated by optimized EC 45cps and HPMC E5 LV combination (4:1 ratio), for evaluating drug release profile.

2. Evaluation of core and functional coated pellets:

- **Drug content:**

Drug containing core as well as final functional coated pellets were evaluated for drug content. Pellets were crushed to powder. Accurately crushed sample equivalent to 120 mg of verapamil HCL was transferred to 100 ml volumetric flask and diluted to 100 ml with water and stirred in a magnetic stirrer for complete dissolution of drug. Solution was filtered, one ml of this solution was taken, diluted to 100 ml with water and absorbance was noted at 278 nm. Drug content was determined using calibration curve.

- **Size Distribution:**

Particle size distributions of drug containing core pellets as well as final layered pellets were evaluated by sieve analysis. One Hundred grams of the pellets were sieved through a nest of sieves 14, 16, 18, 20, 30, 40 and pan the percentage weight distribution was determined.

- **Friability:**

Drug containing core pellets as well as final pellets were evaluated for friability. The friability of the core pellets was determined as % weight loss after 200 revolutions of 10 g of pellets in a Friabilator (Erweka, Germany).

- **Scanning electron microscopy:**

The pellets from selected batches of the formulation were sputter coated with gold for 5 min. Surface topography of the pellets were determined using environmental scanning electron microscope (Jeol JSM 840 SEM) at TIFR Mumbai. The samples were placed on tab using adhesive gum. The tab was then placed on stage and vacuum was applied (pressure 0.98 torr). Samples were scanned using secondary electron beam (15kV) and photographed to assess their surface appearance and shape. A large field detector was used to analyze the signals.

- **Physical properties:**

Final layered pellets were evaluated for its physical properties such as Angle of repose, Bulk density, Tapped density, Hausner's ratio and Carr's index.

- ***In-vitro* Drug Release Studies:**

The dissolution studies of the pellets equivalent to 120 mg of verapamil HCL were performed using USP XXIII type I dissolution test apparatus. Volume of dissolution medium was 900 ml with a stirring speed of 75 rpm and temperature of medium was

maintained at 37.0±0.5°C. These conditions were kept constant for all dissolution studies. The drug release study was carried out in 0.1 N HCl (pH 1.2) for 2 hrs, later release studies were carried out for 4.5 hrs in phosphate buffer pH 6.8 and finally in phosphate buffer pH 7.4 till complete release of drug. Verapamil HCL concentrations were determined by UV spectrophotometry at a wavelength of 278 nm. Percent drug dissolved at different time intervals were then calculated.

G. INNOVATOR Details for release study:

Brand name - Verelan PM 300mg

Generic name - Verapamil Hydrochloride Extended Release Capsules, 100 mg

Label claim - Each capsule contains Verapamil Hydrochloride, USP 100 mg.

Batch no. - 6D276

Manufactured by- Schwarz Pharma , Inc USA

Marketed by - Elan Holdings, Inc.

Pack - HDPE Bottle of 100 capsules

Result & Discussion

The core pellets of Verapamil HCL were prepared using organic acids as pH-adjuster and microcrystalline cellulose as diluent by extrusion-spheronization method. Different ratios of drug: fumaric acid: MCC a shown in Table 1. For preparation of core pellets. PVP-K30 in water was used as binder in the preparation of the pellets. Batch A1 and B4 fails to produce better extrudates as well as spherical pellets while A2, A3 and B3 produced spherical pellets showing better physical properties.

Table 1: Composition of core verapamil HCL pellets

Sr. No	Ingredients in mg	A	A1	A2	A3	A4	B1	B2	B3	B4
1	VerapamilHCl	120	120	120	120	120	120	120	120	120
2	Fumaric Acid	-	80	100	120	140	80	100	120	140
3	MCC(Avicel pH 101)	180	100	80	60	40	100	80	60	40
4	Polyvinyl Pyrrolidone(PVP K30)	12	12	12	12	12	12	12	12	12
5	Water	qs.	qs.	qs.	qs.	qs.	qs.	qs.	qs.	qs.

Formulation A without organic acid, Formulations A1-A4 with Fumaric acid, Formulations B1-B4, with malic acid

a.) Drug content:

For Batches A, A1-A4 and B1-B4 drug containing core pellets showed % drug content within the Official specification limits. Hence these batches were preceded for further processing. Among all batches, batch A, A4 and B4 revealed less drug content (Table 2). In coated pellets of the same batches, drug content was found to be more as compared to other batches but almost all batches were within the official specification limits.

Table 2: Drug content of final functional pellets

Sr. No.	Batches	Drug content (%)	Drug Content after Coating (%)
1	A	91.62	94.33
2	A1	95.72	99.54
3	A2	96.25	99.78
4	A3	98.21	100.26
5	A4	94.52	96.25
6	B1	96.46	98.99
7	B2	96.21	98.71
8	B3	94.39	97.58
9	B4	92.96	96.58

b.) Size Distribution

The particle size distribution is shown in Fig. 1. The dominant size (maximum size) fraction of drug containing core pellets was 0.84 -1.40 mm and that of the layered pellets was 1.21-1.69 mm for batch A3. Fumaric acid is pH-adjuster having good spheronizing property. Formulations containing fumaric acid showed uniform pellets as compared to other batches containing malic acid and its different concentrations revealed variations in size distribution of core pellets.

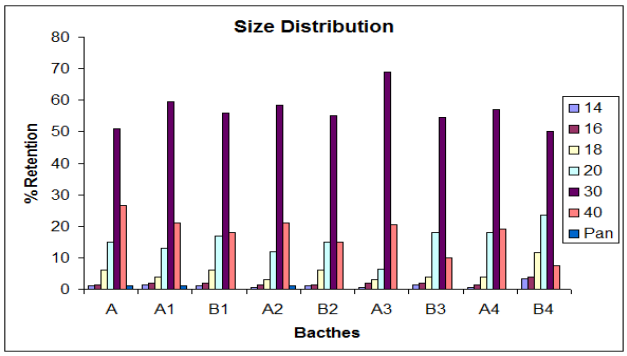

Fig. 1: Size distribution of the verapamil HCL pellets (determined by sieve analysis).

c.) Friability

The friability of the drug containing core pellets was found to be 0.09 ± 0.005%. This indicated that the core pellets were quite hard and able to withstand the mechanical stresses of the subsequent process. The friability of the final layered pellets was 0.07 ± 0.002% which indicates that they can withstand handling, shipping, storage and operation like filling. The friability of batch A and B1 to B4 core pellets was more than batch A1to A4 core pellets, it may be because of malic acid (B1-B4) is not spheronised well as compare to fumaric acid (A1-A4).

d.) Scanning electron microscopy of core pellets (SEM)

SEM images of verapamil HCL core pellets showed that non-aggregated pellets with regular spherical shape were obtained in all A1 to A4 formulations and in B2 and B3 formulations. The lacks of sphericity observed for all B1 to B4 formulations may be because of malic acid have poor spheronizing property as compared to fumaric acid. Fig. 2.A shows the appearance of external morphology of the core pellet (with Fumaric Acid) under SEM. The core pellets were spherical agglomerates with a slightly rough surface. Fig. 2.B showed surface of the coated pellets was smoother than the core pellet. Fig. 2C shows surface morphology of the core pellet (with Malic Acid) having uniform rough surface Fig. 2D is the section of a functional coated or extended release coated pellet which shows the uniformity of the coating.

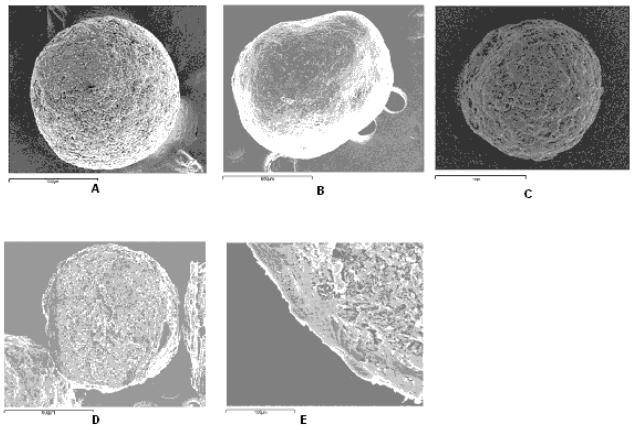

Fig. 2: is the section of layered pellet in which uniform layer of coating agent is deposited during the layering process.SEM image of functional coated core Verapamil HCL pellets (only for selection of core pellets for coating optimization). A) Core pellet obtained by using fumaric acid B) Coated pellet C) Core pellet obtained by using malic acid D) Section of a functional coated pellet E) Uniformity of coating agent layer.

e.) Physical properties:

The core pellets were evaluated for its physical properties for the following parameters shown in Tables 3 and 4. The pellets possessed better physical properties as per specifications. The densities of pellets were being taken in to consideration not only for technological purposes, but also because the majority of pellets fill in the capsules and thus for these fixed volume dosage forms the density will determine the fill weight. In addition, this physical property could have an influence on the gastric emptying times if it exceeds a limiting value above

2400 kg/m^3. Observed densities of pellets matched with fill weight of capsule.

Table 3: Evaluation of physical properties of final functional pellets

Sr. No.	Physical properties	Values(n=3 ± SD)
1	Angle of repose	27.66 ± 1.52
2	Hausner's ratio	0.9255 ± 0.0108
3	Carr's index (%)	7.39 ± 1.105

Table 4: Evaluation of physical properties of final functional pellets

Sr. No.	Batches	Bulk Density	Tapped density
1	A	0.78	0.85
2	A1	0.69	0.77
3	A2	0.73	0.78
4	A3	0.77	0.80
5	A4	0.72	0.74
6	B1	0.70	0.75
7	B2	0.69	0.74
8	B3	0.67	0.72
9	B4	0.66	0.70

f.) In-vitro drug release of verapamil HCL from final coated pellets:

From the different percentile coating desirable extended release (more than 80% in 24 hrs) could be achieved by each and every coated formulation in pH 6.8 and pH 7.4. Also no burst release was observed in pH 1.2. Batch A3a16% formulation matched with Innovator formulation in which pellets coated by EC 45cps: HPMC E5LV (4:1) coating (Fig. 3). With 12% and 14% coating burst release was observed in initial 5 hrs but for 16% and 18% coating, consistent extended release with better pattern was observed. From Fig. 4, it can be observed that, release profile of pellets coated by EC 20cps: HPMC E5LV (4:1) was extended with increase in percentile coating but release profile does not match with Innovator release. Pellets (A3c) coated by Eudragit RS 100: Eudragit RL 100 (9:1) had similar release pattern as that of batch A3b but drug release profile was not matched with innovator formulation. However pellets coated by Eudragit NE30D (A3d) reveals smoother release profile than all other batches (A3a, A3b and A3c). Release pattern of A3d22% coated formulation matches with innovator formulation. From all coated formulation, it was observed that, A3a and A3d coated formulations had better release pattern than A3b and A3c formulations. Thus, it could be concluded that EC 45cps: HPMC E5LV (4:1) and Eudragit NE30D coated pellets with microenvironment provided by fumaric acid demonstrated better release profile.

Table 5: In-vitro Release of Pellets Coated with EC-45cps: HPMC-E5LV (4:1) (A3a)

%Cumulative Release of Verapamil HCL				
Time	A3a12%	A3a14%	A3a16%	A3a18%
1	6.67	6.44	6.22	2.64
2	16.97	15.21	13.09	7.70
4	45.33	43.99	40.09	33.29
8	53.28	52.14	52.47	48.55
11	70.40	65.86	62.43	58.75
14	76.46	75.34	73.56	70.06
18	94.10	84.02	82.22	79.74
24	95.72	97.88	97.13	93.83

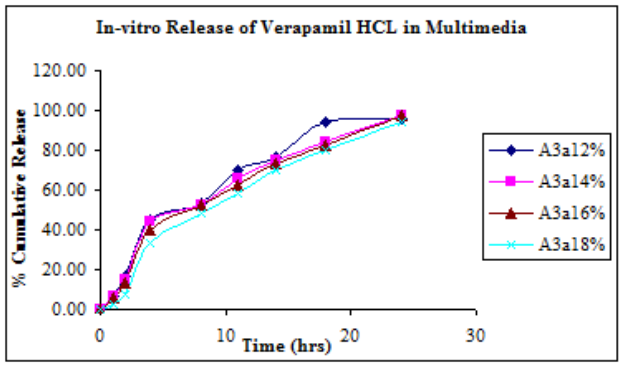

Fig 3. In-vitro release of verapamil HCL in multimedia

Table 6: In-vitro Release of Pellets Coated with EC-20cps+HPMC-E5LV (4:1) (A3b)

%Cumulative Release of Verapamil HCL				
Time	A3b18%	A3b20%	A3b22%	A3b24%
1	6.67	4.63	3.21	2.64
2	11.32	9.75	8.97	6.54
4	25.89	21.06	19.96	18.12
8	46.08	41.33	38.62	37.86
11	60.25	57.15	52.68	50.33
14	69.42	66.88	60.09	58.10
18	84.15	81.23	78.98	75.91
24	97.92	97.56	96.84	93.79

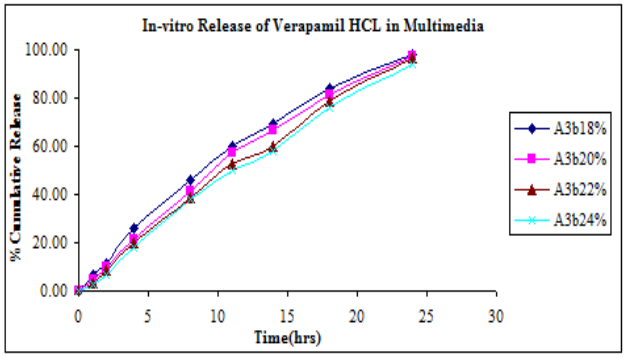

Fig. 4. In-vitro drug release of batch A3b formulations.

From all above observations of coated formulation, A3a16% and A3d22% showed better release pattern with extended release upto 24 hrs and release pattern of both formulations matched with innovator formulation (Fig. 5).

Table 7: Cumulative Release of Verapamil HCL

Comparative %Cumulative Release of Verapamil HCL			
Time	A3a16%	A3d22%	Innovator
1	6.22	6.01	6
2	13.09	13.98	13
4	40.09	40.22	40
8	52.47	52.68	50
11	62.43	59.98	62
14	73.56	67.07	73
18	82.22	78.30	82
24	97.13	98.35	94

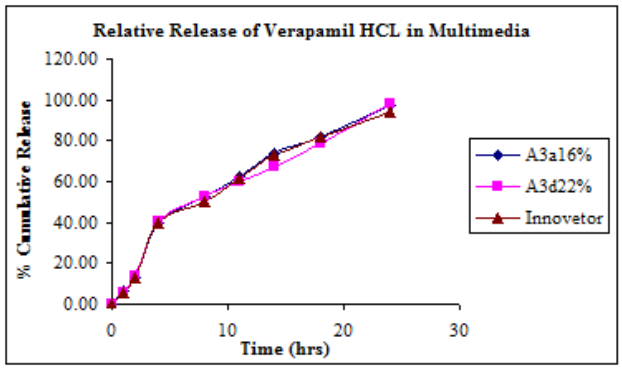

Fig. 5: Comparative In-vitro drug release of batch A3a16%, A3d22% and innovator (Veralan PM 300 mg Capsule) formulations.

Conclusion

Weakly basic drugs demonstrate higher solubility at low pH thus often leading to faster drug release at lower pH, verapamil HCl being weakly basic was selected as model drug as its solubility decreases in intestinal pH and leads to decrease in bioavailability of drug. The objective of this study was to achieve pH-independent release of weakly basic drugs from extended release formulations based on the organic acids used in core pellet. Pelletization technique was selected for the formulation of verapamil HCl to reduce the inter individual variations in plasma levels. PH-independent drug release was achieved from pellets consisting of organic acid in their core when coated with selected pH-independent coating polymers like ethylcellucose, hydroxypropylmethyl cellulose and Eudragit polymers. Organic acids are pH-adjuster at higher pH. Therefore, they are able to compensate the poor solubility of weakly basic drugs at high pH. This approach was successful by using organic acids that demonstrates create microenvironment at higher pH. The addition of fumaric acid to core of the pellets created the microenvironmetal pH within the pellets thus increasing the solubility of the weakly basic drug at higher pH.

Acknowledgement

References

1) Susan A. Charman and William N. Charman. Oral Modified Release Delivery Systems. In: M.J.Rathbone Ed. Modified Release Drug Delivery Technology, New York; Marcel Dekker, vol 126, page no-1-10, (2003).
2) Bodmeier, R.; Paeraakul, O. Suspensions and dispersible dosage forms of multiparticulates. In Multiparticulate Oral Delivery, 1st Ed.; Ghebre-Sellassie, I., Ed.; Marcel Dekker: New York, 1994; (65), 143-158.
3) Sandberg, A.; Blomqvist, I.; Jonsson, U.; Lundborg, P. Pharmacokinetic and pharmacodynamic properties of a new controlled-release formulation of metoprolol: a comparison with conventional tablets. Eur. J. Clin. Pharmacol., 1988, (33) (Suppl.), S9–S14.
4) Ghebre-Sellassie Pellets: A General overview, in Pharmaceutical Pelletization Technology, (Ghebre-Sellassie, and Ed.), Marcel Dekker, New York, 1989, pp. 1-12.
5) Erkoboni, D.F. Extrusion/Spheronization. In Pharmaceutical Extrusion Technology, 1st Ed.; Ghebre-Sellassie, I., Martin, C., Eds.; Marcel Dekker: New York, 2003;(133), 277-322.
6) Nellore, R.V.; Rekhi, G.S.; Hussain, A.S.; Tillman, L.G.; Augsburger, L.L. Development of metoprolol tartrate extended-release matrix tablet formulations for regulatory policy consideration. J.Contr. Rel., 1998, 50 (1-3), 247-256.
7) pH-independent release of a weakly basic drug from water-insoluble and -soluble matrix tablets; A. Streubel, J. Siepmann, A. Dashevsky and R. Bodmeier; College of Pharmacy, Freie Universität Berlin, Kelchstr. 31, 12169 Berlin, Germany; Journal of Controlled Release; Volume 67, Issue 1, 15 June 2000, Pages 101-110.
8) Jenny Bryan, The Pharmaceutical Journal. 2005; 274:90.
9) J. M. Newton, New Developments in pellets, European J. Pharm. and Biopharm. (1999) 39-44.
10) C. Rodriguez, J. J. Torroada, Micromeritic and Packaging Properties of Diclofenac Pellets and Effects of some formulation variables, Drug Dev. Ind. Pharm. 27 (2001) 847-855.