Preparation and *in vitro* Evaluation of Sustained Release Drug Delivery System for Verapamil HCl

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Verapamil HCl is a calcium channel blocker administered on thrice a day dosage regimen. In the present study resinates of verapamil HCl were formulated using Indion resins. Drug loading process was optimized with respect to drug:resin ratio, pH of loading solution, and particle size of resin. Resinates were characterized using XRPD. *In vitro* drug release rates from resinate was not adequately sustained. Hence resinates were incorporated in pellets using extrusion spheronization to achieve desired release pattern. Optimum drug loading was seen at pH of 3.5 in drug resin ratio of 1:1 and was seen to increase with temperature. XRPD studies revealed verapamil to be present in amorphous form in resinates. Drug release from resinates was complete in four hours. Resinates were pelletized using hydroxypropylmethylcellulose. Resinate of Indion 254 with 5% hydroxypropylmethylcellulose fulfilled USP criteria for extended release verapamil preparation.

Key words: Verapamil, sustained release drug delivery system, Indion 244, Indion 254

Ion exchange resins have versatile properties as drug delivery vehicles and have been extensively studied in the development of novel drug delivery systems[1]. Cation exchange resins containing strong sulfonic acid group form a strong bond with cationic drugs and elution of drug from resinates is slower[2]. Formulations based on ion exchange resins are successfully marketed viz Pennkinetic system by Pennwalt Corporation, USA, marketed as Pentuss®. It contains codeine and chlorpheniramine, both complexed with cation exchange resin, where the chlorpheniramine resinate is uncoated and codeine resinates particles are coated with release controlling ethyl cellulose membranes[3]. Sustained release resinate of 5-fluorouracil[4], chlorpheniramine maleate[5] and phenylpropranolamine[6] have been described. Micro particulates of ion-exchange resin drug complex have also been used for ophthalmic drug delivery of betaxolol, an antiglaucoma agent[7]. Manek and Kamat[8] evaluated Indion CRP–244 and CRP–254 resins as sustained release and taste masking agents. In these systems, drug loaded on the resin dissociates slowly in GI fluids to give sustained release and resinates are incorporated in matrix to retard the release[9]. Physical mixture of drug and ion exchange resin form complex *in situ* which release drug with same rate as preformed resinates[10]. Attempts to coat resinate with rate controlling barrier have successfully obtained controlled release[11,12]. Objective of present work is to prepare sustained release resinates of verapamil HCl. Resinates are further pelletized by extrusion spheronization obtain desired release.

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MATERIALS AND METHODS

Verapamil HCl was a gift from Nicholas Piramal (I) Ltd. Indion 244 and Indion 254 were provided by Ion Exchange India Ltd. Microcrystalline cellulose was gifted by Chemfield Pharma, Nagpur and hydroxypropylmethylcellulose (15 cps) was gifted by Zim Laboratories, Nagpur. Verapamil was analyzed using UV/Vis spectrophotometer Shimadzu (model-1601), solutions were prepared in buffer pH 1.2 and pH 6.8 at 278 nm.

Preparation of drug resin complexes (resinates):
Resinates were prepared by batch process. Accurately weighed amount of verapamil HCl (about 1g) was taken and dissolved in 100 ml of distilled water. A known weight of ion exchange resin was added to this solution and was stirred on a magnetic stirrer. Time

to reach equilibrium was determined by periodically measuring concentration of the drug in solution. Resinate thus formed was filtered, washed with deionised water and dried at 50°. Drug content of loading solution was determined spectrophotometrically at 278 nm. The difference in drug content of loading solution before and after loading was taken as drug loading.

Effect of pH on drug loading:
Two sets of solutions were prepared containing about 1 g of verapamil HCl in 100 ml water. The pH of solutions was adjusted at 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0 and 6.5. Indion 244 and Indion 254(1g) were added and solution was stirred on a magnetic stirrer for 4 h. Resinate was filtered and drug content remaining in loading solution was determined

Selection of drug: resin ratio and effect of temperature on drug loading:
Four batches containing drug-resin in the ratio of 1:1, 1:1.5, 1:2 and 1:3 were prepared with Indion 244, Indion 254. The pH of drug solutions was maintained at pH 3.5. After stirring for 4 h resinate was filtered and drug content remaining in loading solution was determined. To study the effect of temperature series of solutions containing verapamil HCl and resin in 1:1 ratio, maintained at pH3.5, were stirred on magnetic stirrer at room temperature, pH 35°, 40°, and 45°. After 4 h, resinates were filtered and washed with deionised water. The drug content remaining in loading solution was determined.

Physical properties of resins and resinates:
Different physical properties of resin and resinates like shape, flow properties, bulk density, tap density, Hausner ratio, packing ability were studied. The X-ray diffraction studies were carried on Phillips analytical X-ray BV (PW1710) using cu anode 40 kv voltage and 30 mA current.

***In vitro* drug release from resinates[13]:**
Resinates of verapamil with Indion 244, Indion 254 were subjected to *in vitro* dissolution studies using USP 24 method. The apparatus used was USP type II at 50 rpm. Dissolution medium was 900 ml simulated gastric fluid (without enzyme) for 1 h and 900 ml simulated intestinal fluid (without enzyme) for 7 h at 37±0.5°.

Formulation of pellets:
Resinates of verapamil HCl with Indion 244 and Indion 254 were formulated into pellets with hydroxypropylmethylcellulose by extrusion–spheronization (Table 1). Parameters employed for extrusion were die roller size 2 mm at 15 rpm and spheronization was carried using cross hatch pattern friction plate, groove size 1mm, spheronizing speed 1000 rpm.

Drug content determination of pellets:
Pellets were crushed; fine powder produced was weighed accurately to get 50 mg drug equivalent quantity and transferred to 2 N HCl. This suspension was then stirred on magnetic stirrer for 4 h, filtered and drug content was determined.

Evaluation of physical properties of pellets[14,15]:
The physical properties of pellets such as shape, size by sieve analysis, bulk density, tap density, Carr compressibility index, friability, flow rate and Hausner ratio of pellets were determined as described in literature.

***In vitro* drug release profile of pellets:**
Pellets formulated with resinates of Indion 244 and Indion 254 were subjected to *in vitro* dissolution studies using USP 24 method for extended release Verapamil preparation.

RESULTS AND DISCUSSION

Time to reach ion exchange equilibrium was found to be 4 h. Results showed difference in loading under different pH conditions reported, maximum drug loading on the resin occurs at pH 3.5. (fig. 1) This may be due to fact that the protonated fraction of verapamil (pKa 8.6) decreases with increase in pH. As ion exchange is an equilibrium process the presence of higher number of ionized drug molecules increases drug loading. Similar findings have been reported earlier[16]. Optimum loading was obtained at drug resin ratio of 1:1 (fig. 2). Increase in the amount of resin increases the amount of drug adsorbed from the solution but decreases drug content/g of resinates.

TABLE 1: FORMULAE FOR PREPARATION OF PELLETS.

Ingredients	Batches						
%w/w	B1	B2	B3	B4	B5	B6	B7
Indion 244 resinate	50	50	50	-	-	-	-
Indion 254 resinate	-	-	-	50	50	50	-
MCC	50	48	45	50	48	45	45
HPMC	-	2	5	-	2	5	5
Verapamil HCl	-	-	-	-	-	-	50

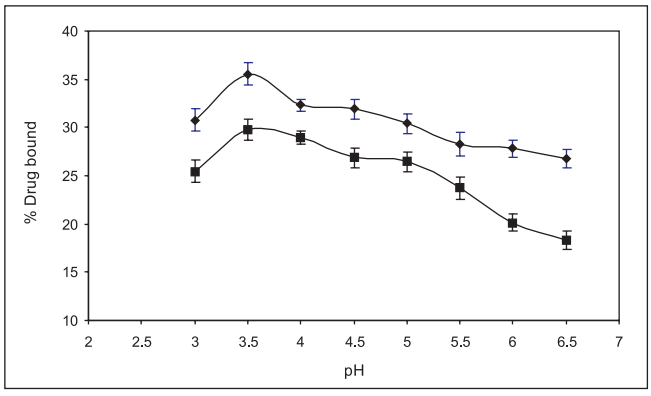

Fig. 1: Effect of pH on loading of verapamil HCl
Effect of pH on loading of verapamil on Indion 244 (—♦—) and on Indion 254 (—■—)

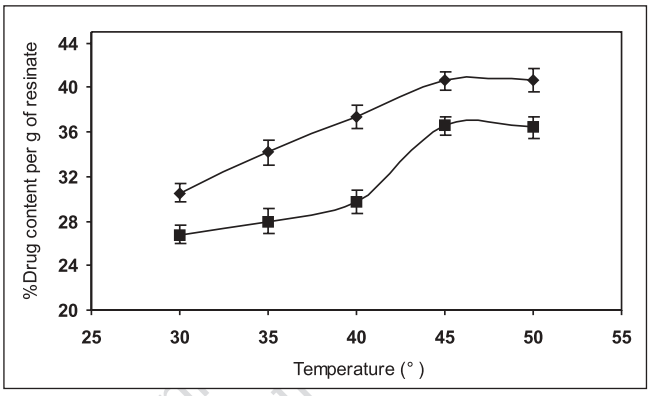

Fig. 3: Effect of temperature on loading of verapamil
Effect of temperature on loading of verapamil on Indion 244 (—♦—) and on Indion 254 (—■—)

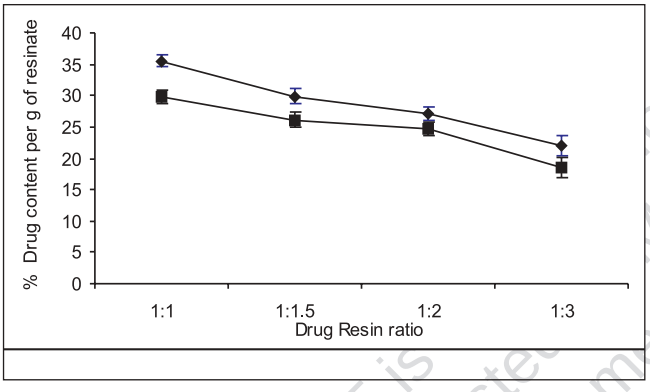

Fig. 2: Effect of drug: resin ratio on loading of verapamil HCl
Effect of drug:resin ratio on loading of verapamil on Indion 244 (—♦—) and on Indion 254 (—■—)

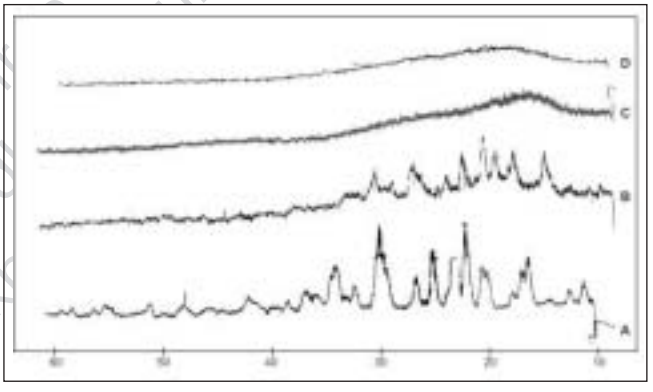

Fig. 4: Powder X-ray diffraction patterns
Powder X-ray diffraction patterns for a) verapamil HCl b) Indion 244, c) physical mixture and d) Indion 244-verapamil resinate

TABLE 2: PHYSICAL PROPERTIES OF RESINS AND RESINATES

Character	Indion 244	Indion 244 Resinate	Indion 254	Indion 254 Resinate
Shape	Irregular	Irregular	Irregular	Irregular
Angle of repose	28.15	28.52	30.71	29.14
Bulk density	0.684	0.595	0.625	0.609
Tap density	0.806	0.694	0.735	0.714
Carr's index	15.13	14.26	14.96	14.7
Hausner ratio	1.17	1.16	1.17	1.17

The results are average of three determinations

Increase in temperature increased drug loading but up to certain extent (fig. 3). This may be due to swelling of resins at increased temperature, which open ionic sites for the exchange of counter ions. Optimum drug loading was seen at 45°. The effect of temperature is more pronounced for poorly water soluble and un-ionizable drugs. Higher temperatures tend to increase the diffusion rate of ions by decreasing the thickness of exhaustive exchange zone. Frank and Koebel[17] reported that cation exchangers are not affected as significantly by temperature changes as anion exchange resins. Physical properties of resins and resinates are summarized in Table 2. The X-ray diffraction shows that crystalline peak characteristic of drug were masked and characteristic amorphous X-ray diffraction pattern of resin was prevalent in complex.

TABLE 3: EVALUATION OF PHYSICAL PROPERTIES OF PELLETS

Batches	% Retained on 12/22 mesh	Mean Pellet diameter	Angle of repose	Flow rate (g/min)	Bulk density (g/cc)	Tap density (g/cc)	Carr's index	Hausner ratio	% Friability
B1	90.25	1125	22.25	27.51	0.82	0.88	6.8	1.07	0.88
B2	91.7	1021	23.12	25.12	0.85	0.91	7.05	1.07	0.49
B3	89.95	1091	24.29	25.64	0.86	0.92	6.52	1.06	0.37
B4	94.22	1004	22.57	27.88	0.79	0.86	8.13	1.08	0.91
B5	91.86	1054	23.33	28.00	0.81	0.86	5.81	1.06	0.55
B6	93.15	1139	22.18	26.86	0.89	0.94	5.65	1.05	0.48
B7	90.81	1210	22.29	27.14	0.85	0.90	5.55	1.05	0.51

The results are average of three determinations

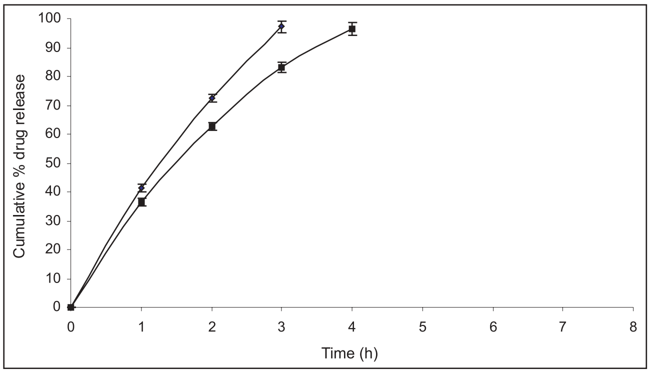

Fig. 5: Dissolution profiles of verapamil from Indion 244 and Indion 254 resinates
Represents *in vitro* dissolution profile of Indion 244 resinate (─♦─) and of Indion 254 resinate (─■─)

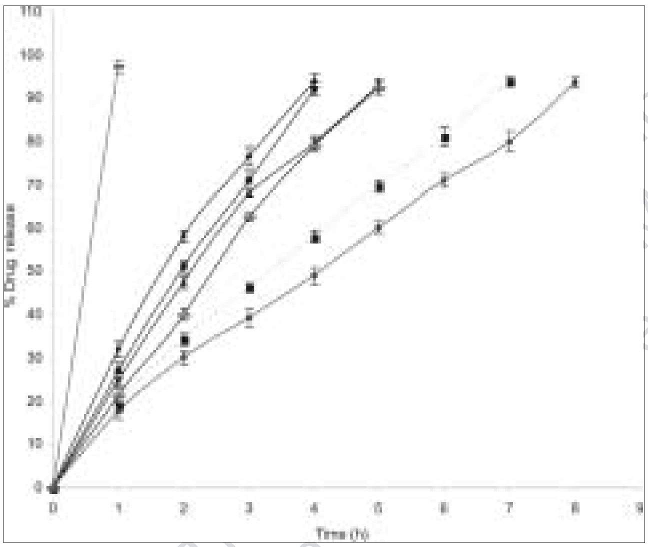

Fig. 6: Dissolution profiles of verapamil from pellets.
***In vitro* dissolution profiles of B1 (─♦─), B2 (─■─), B3 (─▲─), B4 (─ ─), B5 (─■─), B6 (─●─) and B7 (─).**

(fig. 4). The characteristic hump shown by a typically amorphous structure of resin was also not seen in drug resinates, and the physical mixture of two showed mixed patterns. Thus it can be concluded that the drug resinate was a chemical complex. Studies have shown that the molecules of the entrapped drug changes from the crystalline to amorphous[18]. The drug release from resinate *in vitro* was fast (fig. 5) with 97.2% of drug released in 3 h from Indion 244 resinates and 98.5% of drug was released in 4 h from Indion 254 resinates. All the pellets formulated were spherical in shape with more than 90% of the pellets retained on 12/22 mesh. It indicates tat pellets were having uniform particle size in the range of 1000-1200μ. The material having angle of repose < 30° have good flowability. Angle of repose of all batches ranged

TABLE 4: DRUG CONTENT OF FORMULATED PELLETS

Formulation	B1	B2	B3	B4	B5	B6	B7
Drug content per 500 mg	105	104	104.5	91	90.5	91.2	249

The results are average of three determinations

TABLE 5: COMPARISON OF DRUG RELEASE FROM B6 WITH USP CRITERIA

Time (h)	Cumulative % drug release	
	USP	Release of batch B6
1	10-21	17.58
2	18-33	30.16
3.5	31-50	44.36
5	50-82	60.33
8	Not less tan 85%	93.81

from 22 to 25°. The flow rate of pellets was also determined which was found in the range of 25 to 28 g/min. From this it can be concluded that pellets have good flow. All batches of pellets have bulk density less than 1.25 g/cm³, which indicate good flow. The Carr's index and Hausner ratio of pellets suggests good compressibility for all the batches of pellets. Friability of all the batches was less than 1%, which was acceptable (Table 3). The drug content of various batches (B1-B7) of pellets formulated was determined (Table 4). The cumulative percent drug release from formulated pellets for 1 h in pH 1.2 buffer and 7 h in 6.8 pH buffer are shown in fig. 6. The results showed that more than 85% of drug was released from pellets formulation of Indion 244 resinate without HPMC in 4 h (batch B1). Addition of 2% HPMC does not affect the drug release significantly (batch B2). By addition of 5% HPMC (batch B3) more than 85% of the drug was released in just 5 h. This may be due to rapid swelling and disintegration of pellets in dissolution medium. The particle size of Indion 244 resinate was comparatively larger because of which dissolution medium penetrates in pellets rapidly and results in disintegration and comparatively rapid drug release. While in case of Indion 254 drug resinate pellets (batch B4) without HPMC more than 85% of drug was released in 5 h, by addition of HPMC in 2% concentration significantly retards the drug release for 7 h. Addition of 5% HPMC (batch B6) retards the drug release for 8 h. This may be because of strong binding properties of HPMC which binds the fine particles of resinate. The drug release from these pellets was simply due to slow erosion and ion exchange. Batch B7 was formulated with pure verapamil HCl with 5% HPMC, releases the complete amount of drug in 1 h which clearly demonstrate the

effect of resinate on drug release. Batch B6 of pellets formulated with 50% Indion 254 verapamil resinate, 45% MCC and 5% HPMC follows USP specifications for extended release verapamil formulation. The drug release from batch B6 followed zero order kinetics with correlation coefficient 0.999.

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