Pharm Res (2010) 27:2106–2118
DOI 10.1007/s11095-010-0212-9

RESEARCH PAPER

Polymethacrylate Microparticles Gel for Topical Drug Delivery

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Received: 22 April 2010 / Accepted: 6 July 2010 / Published online: 24 July 2010

ABSTRACT

Purpose Evaluating the potentials of particulate delivery systems in topical drug delivery.

Methods Polymethacrylate microparticles (MPs) incorporating verapamil hydrochloride (VRP) as a model hydrophilic drug with potential topical clinical uses, using Eudragit RS100 and Eudragit L100, were prepared for the formulation of a composite topical gel. The effect of initial drug loading, polymer composition, particularly the proportion of Eudragit L100 as an interacting polymer component, and the HLB of the dispersing agent on MP characteristics was investigated. A test MP formulation was incorporated in gel and evaluated for drug release and human skin permeation.

Results MPs showed high % incorporation efficiency and % yield. Composition of the hybrid polymer matrix was a main determinant of MP characteristics, particularly drug release. Factors known to influence drug release, such as MP size and high drug solubility, were outweighed by strong VRP-Eudragit L100 interaction. The developed MP gel showed controlled VRP release and reduced skin retention compared to a free-drug gel.

Conclusion Topical drug delivery and skin retention could be modulated using particulate delivery systems. From a practical standpoint, the VRP gel developed may offer advantages in a range of dermatological conditions, in response to the growing off-label topical use of VRP.

KEY WORDS polymethacrylates · topical drug delivery · microparticles gel · verapamil

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INTRODUCTION

Microparticles (MPs) are effective as a versatile carrier for controlled delivery of a wide range of drugs and bioactive substances. Apart from controlling drug delivery, MPs offer several advantages, such as established preparation methodology (1), higher % incorporation efficiency (% IE) compared to nanoparticles, protection of the encapsulated active agent from external influences and higher value for systems based on economic polymers. Drug release from MPs could be modulated by changing the properties of MPs and the polymers used, offering great diversity for several applications (1, 2). MPs have therefore been considered for all routes of administration (3–5) including topical delivery to the skin for various dermatological purposes (6,7).

Topical microparticulate carriers, controlling the delivery of drugs and cosmetic actives to the skin, offer great potentials compared to conventional dermatological vehicles. A fundamental shortcoming of the latter formulations is the provision of topically active agents in relatively high concentrations to the skin with a limited duration of action, resulting in cycles of short-term overmedication and long-term undermedication. In addition, adverse cutaneous reactions may occur as a result of direct skin contact or skin penetration of active agents. In contrast, microparticulate delivery systems allow progressive delivery of active ingredients into the skin along with a favorable tolerability profile (6), reducing irritation while maintaining activity. Topical formulations based on MPs also reduce the potential of systemic adverse effects by decreasing skin permeation (8). They enhance the physical and chemical stability of encapsulated active ingredients (9) and allow their use at lower concentrations but with better homogeneity (10).

Drug carriers for skin delivery are usually incorporated in conventional dermatological vehicles such as gels, creams, or

lotions. The potentials of these composite controlled delivery formulations have been successfully demonstrated in a range of marketed products, which include among others, tretinoin MP gel (Retin A Micro, OrthoNeutrogena, Skillman, New Jersey), 5-fluorouracil cream (Carac, Dermik, Bridgewater, New Jersey), hydroquinone with retinol cream (EpiQuin Micro, SkinMedica, Inc.) and Benzoyl peroxide in both MP cream and MP wash formulations (NeoBenz Micro, SkinMedica, Inc., Carlsbad, California) in addition to a wide range of personal care products containing sunscreen agents, moisturizers and other cosmeceuticals.

Various polymers have been used for the formulation of microparticulate topical delivery systems, including gelatin (6), poly(L-lactide)/polyethylene glycol—poly(L-lactide) (11), poly(lactide-co-glycolide) (12), Eudragit (13) and chitosan (14). Polymethacrylates or Eudragit© polymers are FDA-approved, safe, non-toxic and economic pharmaceutical excipients widely used in the pharmaceutical industry. The wide range of Eudragit polymers, differing in charge, solubility and water permeability, allows for custom-tailored release characteristics enabling a wide range of alternatives to achieve the desired drug delivery performance (9). Moreover, the flexibility to combine different polymethacrylate polymers offers a better control on drug release behavior (15), especially in case of drug methacrylate polymer interaction (16).

Verapamil hydrochloride (VRP), a calcium channel blocker, has been selected as a model hydrophilic drug. Selection was justified by evidence-based literature reports indicating the use of VRP in the treatment of dermatological disorders (17), such as Peyronie's disease (18), wounds (19) cellulite (20) as well as burns, hypertrophic scars and keloids (21). The use of 4–5% VRP in a cream base applied topically on a dermal scar was shown to prevent rebound scarring from the trauma of intralesional injections (22), and a topical VRP gel was found to be effective in Peyronie's disease (23,24). However, topical application of calcium channel blockers is known to result in undesirable cutaneous effects that range from exanthems to severe adverse reactions (25). This is in addition to the liability of VRP to photo-oxidation (26,27), and the need for a sustained drug effect for long-term therapy in certain dermatological makes VRP a good candidate for microencapsulation.

The aim of this study was, therefore, to develop a topical controlled-release gel formulation based on polymethacrylate MPs using VRP and Eudragit RS100 as a neutral polymer matrix. In an earlier study (28), we reported multivariate modeling of the encapsulation and release of VRP using Eudragit RS100 MPs using a multiple emulsion W/O/W method. MP characteristics proved to be affected by several formulation variables, mainly the pH of the external aqueous phase, and their interactions as indicated by artificial neural network and factorial analysis. In the present study, a simple O/O emulsification technique was used to investigate the effect of the formulation variables: initial drug loading, polymer composition (the proportion of an interacting anionic polymethacrylate Eudragit L100 in the polymer matrix), and hydrophilic-lipophilic balance (HLB) of sucrose stearate (SS) dispersing agent on the characteristics of VRP-loaded MPs. The skin permeation of VRP from a selected polymethacrylate MP formulation as a permeation retardant in a 2% HPMC gel was tested using *ex vivo* human skin. Data were compared to those for a conventional gel formulation containing free VRP and for a physical admixture with commercially available plain liposomes to reduce stratum corneum resistance to drug diffusion.

MATERIALS AND METHODS

Materials

VRP and Eudragit L100 (Röhm Aldrich, Germany) were kindly provided by El-Pharaonia Co., Alexandria, Egypt. Eudragit RS100 (Röhm Aldrich, Germany) was a gift from EIPICO, Alexandria, Egypt. Samples of SS with HLB 7, 11 and 15 were kindly provided by Mitsubishi-Kagaku Co., Japan. Liposome base (Fluka, Sigma-Aldrich Chemie Gmbh, Germany). All other reagents were of analytical grade and used as received. Spectra/Por® 2 dialysis membrane 12,000–14,000 Da molecular weight cut-off (Spectrum Laboratories Inc., USA). Human skin was provided by the Department of Plastic surgery, Faculty of Medicine, Alexandria University.

Formulation of Polymethacrylate VRP-Loaded MPs

VRP-loaded Eudragit MPs were prepared using an O/O emulsification solvent evaporation technique (29). VRP and the polymer (Eudragit RS100, Eudragit L100 or a blend thereof) were dissolved in 4.2 ml acetone-methanol mixture (11: 1), a ratio reported previously by Horz *et al.* (29). SS, 3% w/v, was added and the mixture sonicated for 5 min. The mixture was then emulsified with 20 ml liquid paraffin by mechanical stirring at 600 rpm (Arrow Engineering co., model 6000, USA). Stirring was continued for 2 h for solvent evaporation and MP hardening. MPs were separated by centrifugation at 660×g for 10 min, washed six times with *n*-hexane, air dried overnight and stored in a desiccator at room temperature (~25°C). Care was taken to protect VRP from photodegradation. A total of twelve formula-

tions (Table I) differing in polymer composition, initial drug loading and HLB of SS were prepared.

Characterization of MPs

Scanning Electron Microscopy (SEM)

MPs were mounted onto metal stubs using double-sided adhesive tape onto which the MPs were sprinkled. The stubs were then coated with gold using a sputter coater. The coated surface was observed under SEM (JEOL, model JFC-1100E, Japan).

Determination of % Yield

Percent yield was calculated using the formula:

$$\%\,\text{Yield} = \frac{\text{Weight of MPs}}{\text{Total weight of solids}} \times 100$$

Determination of % Incorporation Efficiency (% IE) and Loading Capacity (LC)

MPs (20 mg) were accurately weighed and dissolved in 10 ml methanol, a common solvent for VRP, Eudragit RS100 and Eudragit L100. The solution was assayed spectrophotometrically at 278 nm with reference to a preconstructed calibration plot for VRP in methanol. The % IE was calculated as follows:

$$\%\,\text{I.E.} = \frac{\text{Actual loading capacity}}{\text{Theoretical loading capacity}} \times 100$$

LC is the weight of drug divided by the weight of MPs.

Size Analysis of MPs

Size analysis was performed using a laser diffraction particle size analyzer (Cilas, model 1064 liquid, France). Inside the apparatus, MPs were suspended in 0.02% w/v Tween 80 solution and sonicated for 3 min at 20 watt prior to measurement. Polydispersity was expressed in terms of SPAN value, calculated from D90%, D50% and D10% (the given percentage values are the percentage of particles smaller than these sizes), supplied by the software of the manufacturer, as follows:

$$\text{SPAN} = \frac{D_{90\%} - D_{10\%}}{D_{50\%}}$$

A lower SPAN value indicates narrower size distribution.

Differential Scanning Calorimetery (DSC)

VRP, Eudragit RS100, Eudragit L100, SS HLB 7, selected VRP-loaded MPs and their respective physical mixtures were thermally analyzed using Perkin Elmer Instruments, U.S.A, model DSC 6. MPs (25 mg) were accurately weighed and placed in hermetically sealed aluminum pans. The temperature range 25–300°C was scanned at a heating rate of 10°C/min after 1 min stabilization at 25°C. Inert atmosphere was maintained by purging nitrogen at a flow rate of 20 ml/min.

Drug Release from MPs

VRP release from MPs was measured under sink conditions using a membraneless method. A quantity of MPs containing 5 mg of VRP was weighed and suspended in 20 ml of the prewarmed release medium,

Table I Formulation Factors and Characteristics of VRP-Loaded MPs

Formula	Eudragit polymer composition	Eudragit L 100-Eudragit RS 100 weight ratio	% Initial drug loading	HLB of SS	% Yield	Actual loading capacity, mg/100mg MPs	% I.E.	Mean diameter, μm	SPAN value
F1	RS 100	–	6.25	7	95.2	4.29 ± 0.18	85.08 ± 3.67	45.7	1.5
F2	RS 100		25.00	7	102.5	14.08 ± 0.40	82.23 ± 2.36	49.2	1.5
F3	L 100		6.25	7	81.4	5.21 ± 0.03	106.03 ± 0.54	165.0	1.2
F4	L 100		25.00	7	93.6	17.10 ± 0.14	99.88 ± 0.81	177.2	2.8
F5	L 100-RS 100	1: 1	6.25	7	97.1	4.18 ± 0.20	85.02 ± 4.07	176.5	1.7
F6	L 100-RS 100	1: 5	6.25	7	82.3	4.69 ± 0.09	95.43 ± 1.83	66.0	1.4
F7	L 100-RS 100	1: 7	6.25	7	91.2	4.37 ± 0.10	88.88 ± 2.00	69.3	1.6
F8	L 100-RS 100	1: 11	6.25	7	92.7	4.64 ± 0.08	94.39 ± 1.56	41.1	1.8
F9	L 100-RS 100	1: 5	12.5	7	96.6	8.96 ± 0.15	95.68 ± 1.62	93.6	1.2
F10	L 100-RS 100	1: 5	25.00	7	100.8	15.85 ± 0.26	92.59 ± 1.55	97.7	1.4
F11	L 100-RS 100	1: 5	6.25	11	95.0	4.62 ± 0.22	94.05 ± 4.45	217.5	1.9
F12	L 100-RS 100	1: 5	6.25	15	102.8	4.36 ± 0.06	88.79 ± 1.29	306.9	1.0

acetate buffer pH 5, containing 0.05% w/v Tween 80 in 50 ml capped Erlenmeyer flasks. This medium was selected to simulate skin surface pH (30) and to ensure sink conditions. The flasks were shaken in a thermostatically controlled water bath (GFL, m.b.h. & Co. D3006, model 1083, Germany) at 37±0.5°C at 50 strokes/min. Samples (2 ml) were withdrawn at scheduled time intervals (0.5, 1, 2, 4, 6 and 24 h), diluted suitably with the same release medium and assayed spectrophotometrically at 278 nm. Samples withdrawn were immediately replaced with an equal volume of fresh release medium at the same temperature. The same procedure was used for the control (5 mg free VRP). Release data presented are the average of 3 runs ± standard deviation.

Release Kinetics

The mechanism of VRP release was primarily determined by subjecting release data to 3 kinetic models based on zero order, first order and Higuchi equations in order to select the equation of best fit.

VRP Microparticle Gel

Preparation of VRP Microparticle Gel

A MP test formulation was selected for the preparation of a 2% w/v HPMC gel. Free drug and drug-loaded MPs were incorporated into the gel base by geometric dilution. A portion of free VRP was incorporated to allow for greater early *in vitro* availability of VRP. Control gel was prepared by dissolving 5% free drug in the gel base. Composition of the test gel formulations is shown in Table II.

Drug Release from Topical Gel Formulations

VRP release from the three test gels (Table II) in acetate buffer pH 5 containing 0.05% w/v Tween 80 was measured under sink conditions using a dialysis method.

Table II Composition of the Gel Formulations Prepared

HPMC[a] gel formulations	Free VRP: MPs-loaded VRP[b]	
	Free VRP	MPs-loaded VRP
Gel 1	1	–
Gel 2	–	1
Gel 3	3	7

VRP concentration in the formulated gels was 5% w/v.

[a] Hydroxypropylmethycellulose; used at 2% w/v concentration

[b] MP test formulation F10

A quantity of gel containing 5 mg of VRP was placed in a round stainless-steel assembly, 16 mm diameter and 3 mm depth designed to hold the gel (Fig. 1). The cup containing the gel sample was carefully covered with a dialysis membrane and presoaked overnight in distilled water. A specially designed stainless-steel ring was used to fix the dialysis membrane. Cups were then immersed in prewarmed 20 ml acetate buffer pH 5 in 50 ml capped Erlenmeyer flasks. The flasks were shaken in a thermostatically controlled shaking water bath at 32±0.5°C at 50 strokes/min. Samples (2 ml) were withdrawn at scheduled time intervals for up to 24 h, suitably diluted with the release medium and assayed spectrophotometrically at 278 nm. Release data presented are the average of 3 runs ± standard deviation. Kinetics of drug release from the gels were also studied.

Ex Vivo Permeation Using Human Skin

The ability of VRP in gel formulations to permeate human skin was assessed *ex vivo* using modified Franz diffusion cells.

Skin Preparation. Full thickness human abdominal skin of female patients aged in their 40s was obtained from the Department of Plastic surgery, Faculty of Medicine, Alexandria University, according to an interdepartmental cooperation agreement. Subcutaneous fat was excised using surgical scissors, shortly after surgical removal of the human skin. The skin was cut into small pieces with a scalpel, washed several times with normal saline, and gently blotted dry between two filter papers; the thickness was measured using a micrometer. The skin pieces were then stored at −20°C until further use. Before the experiment, the skin was allowed to thaw until it reached room temperature, then kept soaked in phosphate-buffered saline, pH 7.4, for 1 hr.

Skin Permeation Study. Permeation of VRP through human skin was tested for gel 1 (5% free VRP) and Gel 2 (5% MPs) formulations (Table II). In addition, the permeation of VRP from a freshly prepared physical blend of VRP (5% w/w) and commercially available plain liposomes was also examined. Experiments were run in modified vertical Franz diffusion cells with a receptor compartment volume of 8 ml. The prepared skin was fastened carefully between the donor and receptor compartments, with the stratum corneum side up and held in place with a clamp. The dermal side of the chamber contained a receptor solution of phosphate-buffered saline, pH 7.4. Accurately weighed amounts of the test gels were gently placed in the donor chambers. The diffusion cells were maintained at 37°C throughout

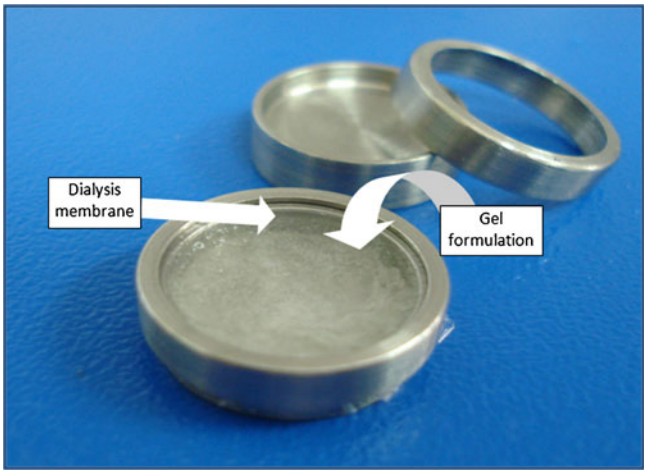

Fig. 1 Round stainless steel assembly used in the *in vitro* release study of VRP from gel formulations.

the experiment using a shaking water bath adjusted at 50 strokes/min. Similarly, diffusion cells, in which the skin was incubated with phosphate-buffered saline, were used as controls for analysis to avoid interference of materials possibly released from the skin in drug determination. Following a 24 h exposure, the skin was removed and the receptor solution collected. The donor compartment and the skin surface were washed several times with methanol. VRP in the donor and receptor chambers was quantified spectrophotometrically at a λ_{max} 278 nm, as reported previously for VRP permeation through guinea-pig and human cadaver skins (31). The % drug retained in the skin was calculated based on the mass balance assumption that the initial amount of VRP in the donor phase was the sum of the remaining drug in the donor phase, the drug retained in the skin, and the drug in the receptor phase (32). Skin permeation experiments were run in triplicate.

RESULTS AND DISCUSSION

The main target characteristics of polymethacrylate MPs intended for topical delivery of VRP as a model hydrophilic drug were high drug loading to reduce the amount of MPs needed, adequate microparticle size that precludes skin absorption and provides acceptable aesthetic properties of the final gel formulation, reduction of direct skin contact with a large amount of the drug, and controlled release of the drug according to a biphasic pattern extending over an in-use relevant period. High incorporation efficiency would be greatly challenged by the hydrophilicity and low molecular weight of the encapsulated drug (33). To enhance drug loading, polymethacrylate VRP MPs were prepared using an anhydrous O/O emulsification solvent evaporation method and SS as dispersing agent. Formulation of VRP MPs with the required properties was based on an investigation of the effect of three formulation variables: polymethacrylate polymer composition (the proportion of an interacting anionic polymethacrylate polymer, Eudragit L100 in the polymer matrix), initial drug loading and the hydrophilic-lipophilic balance (HLB) of SS used at a 3% level. The SS concentration was selected based on reported data (34). However, information on the effect of SS HLB on MP characteristics is lacking. Twelve test formulations were generated. Their composition and characteristics are shown in Table I.

Characterization of Polymethacrylate VRP MPs

Morphology of VRP MPs

SE micrographs of VRP-loaded MPs prepared with either Eudragit RS100 (F1, A1-3) or Eudragit L100 (F3, B1–3) at 6.25% drug loading are shown in Fig. 2. The morphology of VRP MPs was strongly dependent on the polymer type. Eudragit RS100 MPs were nearly ovoid and non-uniform, while those prepared with Eudragit L100 were more uniform spheres. In general, MPs showed no surface-deposited drug crystals and a rough uneven surface with deep grooves. Surface characteristics of MPs are the result of the interplay of preparation conditions including the emulsification method (35) and solvent type (36). Differences in morphological characteristics of MPs made of Eudragit RS100 and L100 could be attributed to differences in viscosity and solvent evaporation rate from their respective solutions in addition to potential interaction of the anionic Eudragit L100 with VRP (37). Eudragit type and concentration were shown to affect the properties of MPs prepared by either emulsification (16) or spray-drying (38) methods. Hybrid MPs prepared with a blend of Eudragit RS100 and Eudragit L100 (1:5) showed similar surface characteristics (Fig. 3). This figure also shows the effect of the HLB of SS (HLB 7 and 15) used as dispersing agent on MP morphology. Increasing SS HLB resulted in the formation of larger and more spherical MPs. Results indicated more efficient emulsification and polymer phase droplet stabilization at the lower SS HLB. The concentration of SS was demonstrated previously to affect the morphology of MPs prepared by O/O emulsification (34). Combined data point to the importance of both the concentration and HLB of sucrose esters in the formulation of MPs by O/O emulsification.

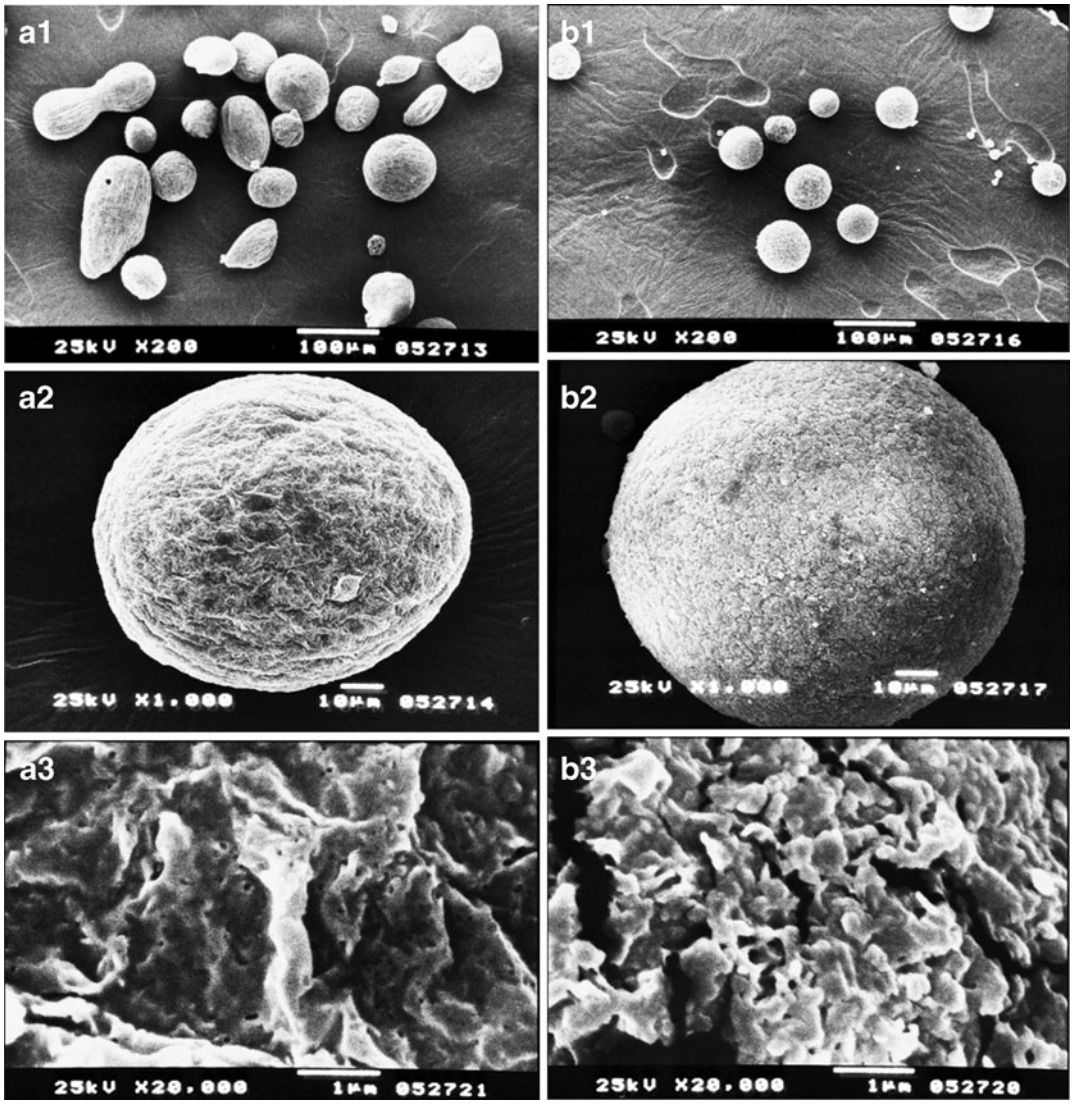

Fig. 2 SE micrographs of Eudragit RS 100 MPs (F1, A1–3), Eudragit L 100 MPs (F3, B1–3) at three magnifications.

Percentage Yield of VRP MPs

The yield of MPs obtained in the study was relatively high (81.4–102.8%, Table I), indicating efficient emulsification with more or less limited loss of MP components.

Size of VRP MPs

The mean size of test MPs ranged from 41 to 306 µm, although it did not exceed 100 µm in most cases. Low SPAN values indicate narrow size distribution, reflecting the formation of a stable emulsion. The size of MPs proved to be mainly affected by the polymer matrix composition and the HLB of SS (Table I). Increasing the proportion of Eudragit L100 in the polymer blend resulted in increased mean particle diameter. Using SS with increasing HLB value produced larger MPs (Table I, Fig. 3), indicating more efficient reduction of internal phase globules at lower SS HLB. Using a dispersing agent with the optimum HLB value in the preparation of MPs would produce finer dispersion and eventually smaller MPs (39). A positive correlation was observed between the HLB value of SS over the range 7 to 15 and the mean size diameter of the prepared MPs (Fig. 4). Such an HLB-MP size relationship could be useful in the preformulation stage of MPs development.

VRP Percentage Incorporation Efficiency (%IE)

The % IE of VRP in MPs was generally high, ranging from 82.2 to 106.0% (Table I), indicating efficient VRP microencapsulation. Elimination of water during MP

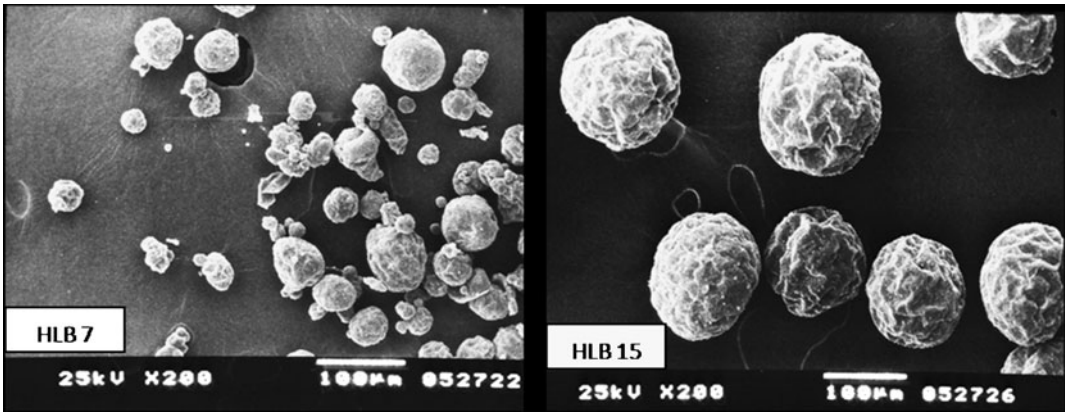

Fig. 3 Effect of HLB of sucrose stearate on the morphology of hybrid MPs (Eudragit L 100:Eudragit RS 100, 1:5).

preparation by O/O emulsification significantly reduces the loss of a hydrophilic drug (40). The % IE exceeded 100% in some formulations (F3 and F4). This can be explained by the loss of very fine poorly drug-loaded or unloaded particles during MP separation or washing (41) or the loss of the dispersing agent to the external phase of the O/O emulsion. Both effects result in a higher proportion of drug to MPs. As the solubility of SS in liquid paraffin does not promote its partitioning to the external phase of the emulsion (34), IE exceeding 100% in this study can be attributed mainly to the loss of fine MPs.

Differential Scanning Calorimetery (DSC)

Possible interaction of VRP with the polymer components and SS of the MP formulations was investigated using DSC at two initial drug loadings: 6.25% and 25% (F6 and F10, respectively). VRP thermogram showed a sharp endothermic peak at 148.93°C corresponding to the melting of the crystalline form of the drug (Fig. 5). This peak was reduced in the physical mixtures and disappeared in thermograms of the two hybrid MP formulations, indicating amorphous dispersion of VRP in the polymer matrix forming a solid solution and drug-polymer molecular interaction, even at the higher drug loading (F10).

VRP Release from MPs

The effect of the three formulation variables (initial drug loading, polymethacrylate polymer composition and HLB of SS) on drug release was investigated. VRP release profiles from MPs at different initial VRP loading were generally biphasic (Fig. 6a-c). Drug release responded differently to initial drug loading, depending on the polymer type and composition of the polymer blend. For instance, release profiles for Eudragit RS100 MPs generally showed a large burst effect and fast drug release at 6.25% and 25% initial drug loading (Fig. 6a), release being slightly faster and complete in 24 h at the higher initial drug loading (≈12% increase at different time points). This suggests entrapment of a higher proportion of drug molecules close to the MP periphery. It has been reported that at higher drug loadings, the path length for drug release is shorter, and the drug closer to the surface leaches out into the release medium, creating empty pores (42). This also enables drug present in the inner core to be released at a faster rate. On the other hand, VRP release from Eudragit L100 MPs was considerably retarded as a result of the drug-polymer interaction. The % drug release at 24 h was only ~20% at 6.25% drug loading. A very slight change was noted at the higher 25% drug loading, pointing to the strong VRP-Eudragit L100 interaction as a primary determinant of drug release. Release profiles of

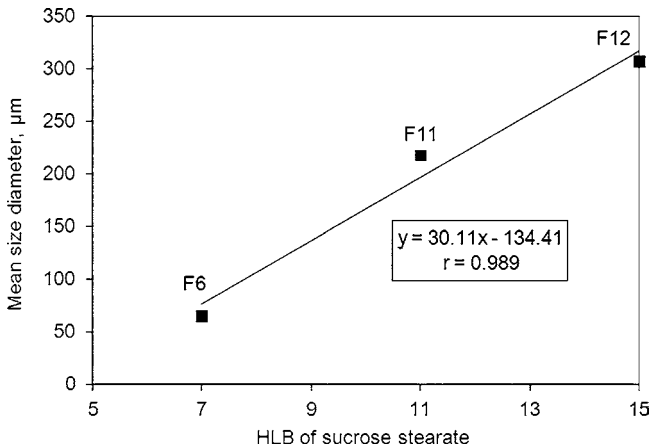

Fig. 4 Effect of HLB of sucrose stearate (SS) on the mean size diameter of VRP-loaded hybrid Eudragit MPs (Eudragit L 100: Eudragit RS 100 1:5) with 6.25% initial drug loading (F6, F11 and F12, Table I).

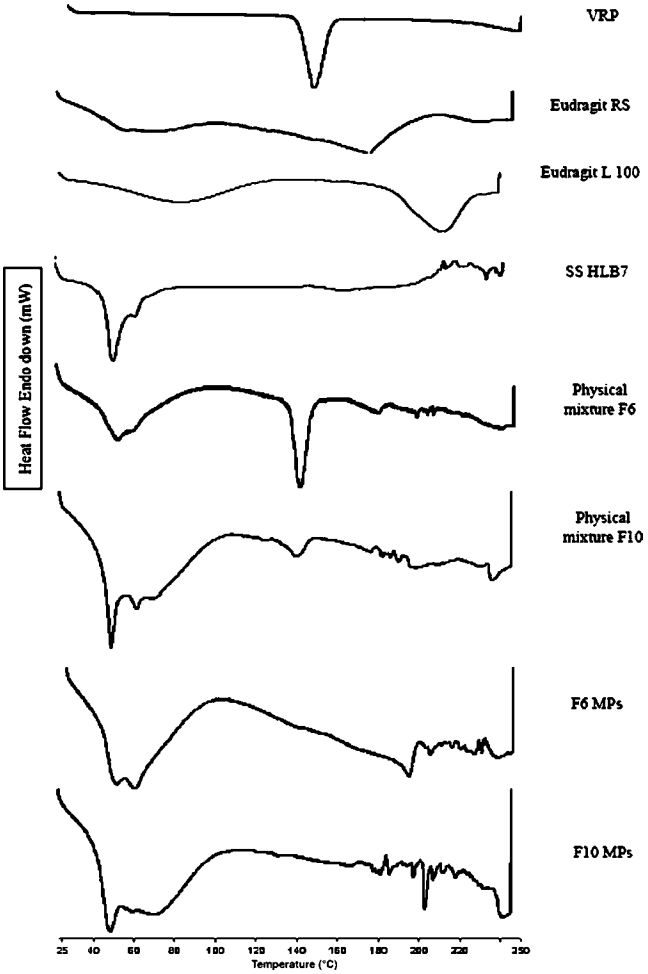

Fig. 5 DSC thermograms of composite MP test formulations F6 and F10 differing in drug content only, their individual components and the respective physical mixture.

MPs prepared with a polymer blend (Eudragit L100 and Eudragit RS100 1: 5) showed changes in burst effect and extent of release in response to initial VRP loading. Release data indicated that modulation of drug release by modifying drug loading could be achieved more effectively when a polymer blend rather than a single polymer component is used for MP formulation, which is consistent with previously reported data (43).

The effect of polymer composition (increasing the proportion of Eudragit L100 in the polymer blend in test MP formulations F5 (1: 1), F6 (1: 5), F7 (1: 7) and F8 (1: 11) is shown in Fig. 7a and b. A wide spectrum of release profiles showing progressive release retardation as the proportion of Eudragit L100 increased was generated. An S shape relationship between polymer composition and % VRP release at 2 h was obtained (Fig. 7b), showing a release retardation dependence on Eudragit L100 concentration, produced by the ionic interaction of VRP with the anionic Eudragit L 100. The performance of weakly basic drugs in sustained release hydrophilic matrices was influenced by a similar polymer, Eudragit L100–55 (44). Advantage can be made of the strong interaction between VRP and Eudragit L100 to modulate the release characteristics of VRP from MPs.

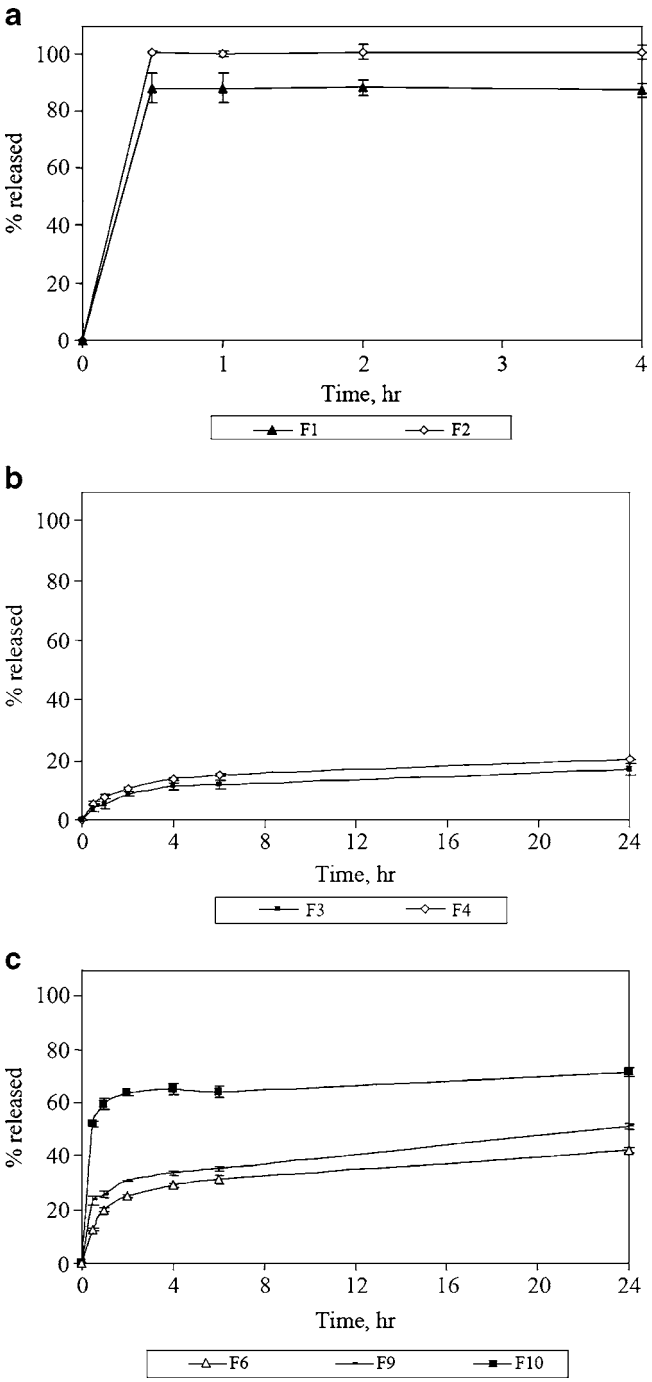

Fig. 6 Effect of initial drug loading on VRP release from MPs prepared using **a** Eudragit RS 100, **b** Eudragit L 100 or **c** Eudragit L 100:Eudragit RS 100, 1: 5 weight ratio as a polymer carrier and SS HLB 7 at pH 5 and 37°C (F1, F3 and F6: 6.25%; F9: 12.5%; F2 , F4 and F10: 25% drug loading).

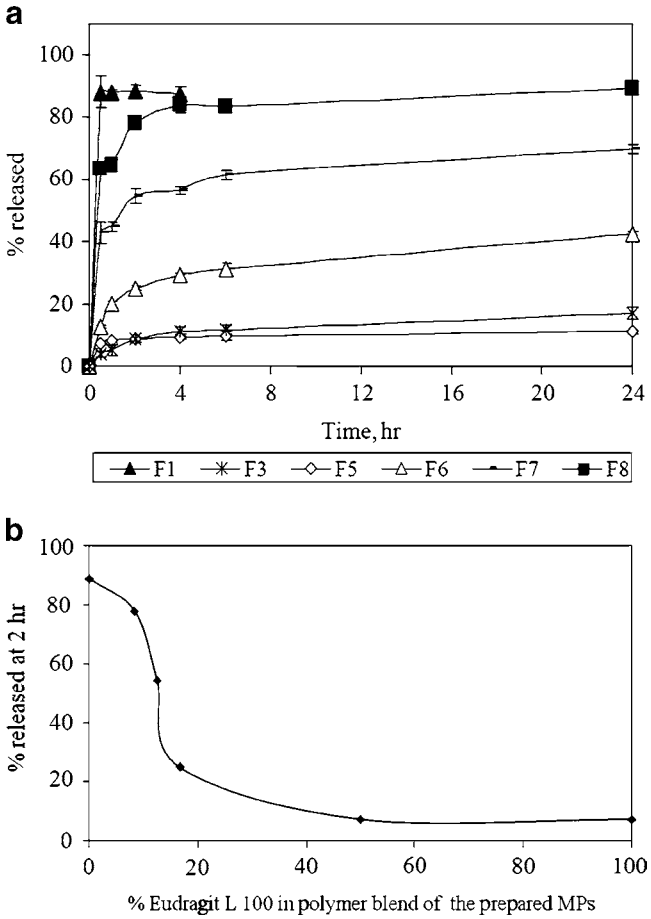

Fig. 7 **a** Effect of polymer composition on VRP release from hybrid MPs (6.25% initial drug loading, SS HLB 7) at pH 5; 37°C. **b** Relationship between % Eudragit L 100 in the polymer blend MPs matrix and % VRP released at 2 h.

The potential effect of HLB of SS (7,11,15) on VRP release from hybrid MPs (Eudragit L100: Eudragit RS100 1: 5) at 6.25% drug loading is shown in Fig. 8. Relatively slow release with a trend of slight enhancement by decreasing the HLB of SS was observed. Although the size of MPs increased proportionately with HLB of SS over the HLB range 7 to 15 (Figs. 3 and 4), this was not reflected on drug release. The strong interaction between VRP and Eudragit L100 appears to offset the effect of size reduction resulting from change in HLB of the dispersing agent on VRP release.

The release kinetics and mechanism were examined by subjecting release data to different mathematical models representing zero-order, first-order and Higuchi's square root of time. The highest correlation coefficient (r) designated the function with the best fit to release data. Correlation coefficients and release rate constants (K) for different models are listed in Table III. The release pattern of VRP from Eudragit MPs for all test formulations corresponded best to the Higuchi equation, indicating a diffusion-controlled release mechanism.

MP Gel for Topical Drug Delivery

Preparation and Drug Release from Topical Gel Formulations

The second objective of this study was to formulate a MP-based gel in 2% HPMC as gel base for topical drug delivery. Referring to data obtained in the formulation section, a test MP formulation (F10) was selected based on good morphological and pharmaceutical attributes (Table I), in terms of high drug loading values (16 mg/100 mg MPs), % I.E. (~93%), yield (100.8%) and adequate size (mean diameter ~98 μm). The release profile of F10 MP test formulation (Fig. 6c) was considered appropriate taking into account further release restriction by the gel base. Three test VRP gel formulations containing 5% VRP were prepared (Table II). These gels contain the drug either in the free form (Gel 1) or as VRP-loaded F10 MPs (Gel 2) or a 3: 7 blend thereof (Gel 3). *In vitro* release profiles in acetate buffer pH 5 at 32°C are shown in Fig. 9. VRP release from Gel 1 resulted in a biphasic release pattern characterized by a relatively fast initial release phase (~50% release at 2 h) and a sustained release phase with almost 100% release in 24 h. Complete release of VRP ensures that the dialysis membrane was not a barrier to drug release. Reduced rate of VRP release from the gel can be attributed to the viscosity of the gel (45). Although Gel 1 sustained the release of VRP because of the gel viscosity (45) and reduced erosion of the gel matrix protected by the dialysis membrane (46), it does not meet other essential requirements for enhanced performance. The relatively fast initial release rate would allow early direct contact of the skin with a relatively large amount of VRP, probably promoting cutaneous reactions and compromising the chemical stability of the drug.

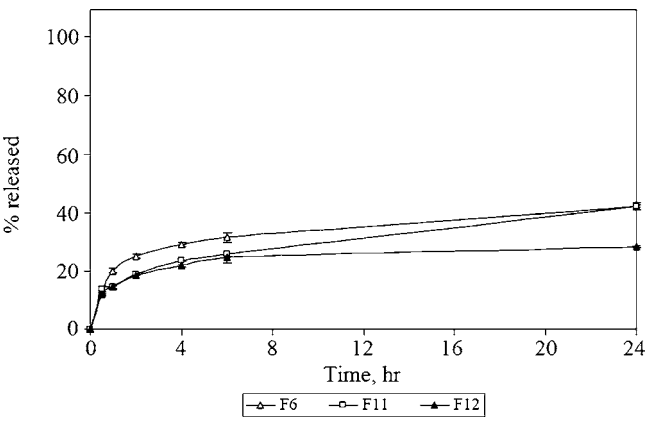

Fig. 8 Effect of HLB of SS (HLB 7, 11 and 15) on VRP release from Eudragit L 100/Eudragit RS 100 (1: 5 ratio) MPs at pH 5 and 37°C.

Table III Release Kinetics of VRP-Loaded Eudragit MPs Prepared

Formula	Zero-order		First-order		Higuchi	
	r	*k*	r	*K*	R	*k*
F3	0.878	0.470	−0.889	0.002	0.954	2.996
F4	0.873	0.528	−0.885	0.003	0.954	3.386
F5	0.856	0.127	−0.860	0.001	0.939	2.221
F6	0.864	0.986	−0.898	0.006	0.944	6.319
F7	0.847	0.952	−0.895	0.010	0.933	6.150
F8	0.879	3.883	−0.900	0.068	0.930	13.123
F9	0.966	1.051	−0.980	0.008	0.991	6.331
F10	0.780	0.571	−0.834	0.007	0.869	3.735
F11	0.970	1.133	−0.982	0.007	0.998	6.843
F12	0.814	0.566	−0.830	0.003	0.916	3.735

K: release rate constant in $mg.hr^{-1}$, hr^{-1} and $mg.cm^2.hr^{-1}$ for zero, first and Higuchi kinetics respectively.

Incorporation of VRP MPs (F10) in the 2% HPMC gel (Gel 2) expectedly resulted in a more progressive drug release with a slower initial release phase (≈20% in 2 h) and lower extent of release (≈50% in 24 h), indicating the efficiency of the reservoir action of the MPs and lack of rapid discharge of the drug into the gel vehicle. This offers advantages such as reduced direct skin contact with a large amount of the drug, thus lowering the potential of skin adverse effects, improving drug stability in addition to minimizing depletion of the MPs before use. Drug release from MP gel could be further modulated using different formulation approaches based either on the delivery system (e.g. use of smaller MPs with larger surface area, polymer matrices with modified composition and porosity, etc.), the gel vehicle (e.g. using different gel matrices, modifying the gel viscosity, pH, etc.) or the drug (e.g. drug concentration, free: loaded drug ratio, etc.). In the present study, incorporating a free-drug fraction (3: 7 "free: loaded" ratio) (Gel 3) enhanced VRP release for all data points (Fig. 9). This approach has been used earlier to modulate the release of dibucaine from liposome gels (47) and naftifine HCl from niosome gels (48). Release data obtained demonstrate the implication of both the microparticulate drug delivery system and the gel vehicle in the pharmaceutical performance of composite gels.

Investigation of drug release kinetics for the three test gel formulations (gels 1–3, Table II) generated data presented in Table IV. Since the correlation coefficients (r) for both first-order and Higuchi diffusion models were high and nearly equal, a more stringent test was needed to define the release mechanism (49). Release rate *versus* % release equations were used. In case of diffusion-controlled release mechanism, the drug release rate (dt versus/dt) is inversely proportional to the % released (Q) (Eq. 1), while in case of first-order kinetics, the release rate is directly proportional to Q (Eq. 2) (49).

$$\frac{dQ}{dt} = \frac{K^2 S^2}{2Q} \tag{1}$$

$$\frac{dQ}{dt} = KW_\circ - KQ \tag{2}$$

where Q is amount of VRP released, K is release rate constant, S is surface area, and $W_\circ$ is initial amount of drug.

The release rate *dt versus/dt* was plotted *versus* Q and $1/Q$. In the case of Gel 1, containing free VRP, plotting VRP release rate *versus* Q resulted in acceptably more linear plot with higher correlation coefficient (Table IV), indicating first-order kinetics. On the contrary, *dt versus/dt versus* $1/Q$ plots were linear with high correlation coefficients throughout the release period for Gels 2 and 3, containing VRP-loaded MPs, suggesting a diffusion-controlled mechanism (Table IV). Accordingly, release of free drug from the gel base followed first-order kinetics, i.e. the drug release rate was proportional to the amount of drug remaining in the gel, in such a way that the amount of drug released per unit time diminished (50). Drug incorporation in MPs resulted in a diffusion-controlled release mechanism. Thus, the release characteristics of MPs as a delivery system formulated in a conventional vehicle appear to be the primary determinant of the drug release kinetics of the composite formulation.

Skin Permeation Study

The permeability of human skin to VRP gel formulations was tested using an *ex vivo* skin permeation experiment. The

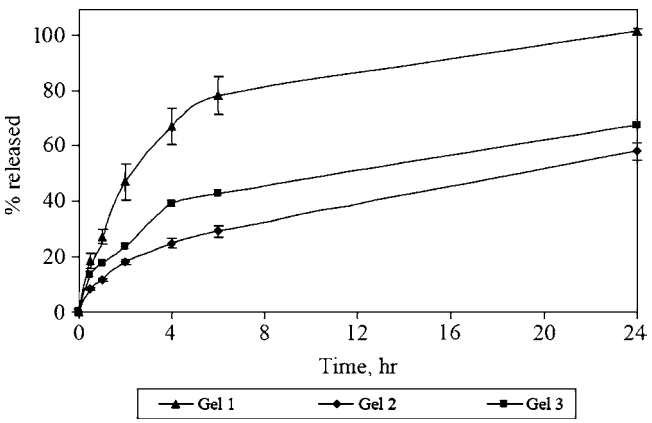

Fig. 9 Release profiles of VRP gel formulations under study at pH 5 and 32°C.

Table IV Release Kinetics of VRP from the Test Gel Formulations

Formula	Zero-order		First-order		Higuchi		Rate dQ/dt *vs* Q	Rate dQ/dt *vs* 1/Q
	r	*K*	r	*k*	r	*K*	r	r
Gel 1	0.824	2.851	−0.997	0.080	0.923	18.725	−0.980	0.932
Gel 2	0.973	1.961	−0.992	0.014	0.999	11.821	−0.865	0.992
Gel 3	0.922	2.069	−0.968	0.017	0.980	12.909	−0.890	0.984

K: release rate constant, $mg.hr^{-1}$, hr^{-1} and $mg.cm^2.hr^{-1}$ for zero, first and Higuchi kinetics respectively

Q: percentage VRP released

potential of modulating VRP skin permeability using a formulation approach was investigated. The gels contained 5% free VRP (control) and 5% VRP entrapped in polymethacrylate F10 MPs as potential permeation retardant. A test formulation containing 5% free VRP in a physical admixture with plain liposomes as potential skin penetration enhancer was also tested. Abdominal human skin from female subjects aged 40 years was used, and the thickness of skin samples was measured to ensure reproducibility of data. The average skin thickness was 2.92±0.34 mm. The experiment was terminated at 24 h to avoid loss of skin integrity. Results are shown in Fig. 10. Treatment of the skin samples with the control gel resulted in 20.2% VRP retention and minimal permeation through full thickness skin at 24 h. Poor skin permeation is attributed to the unfavorable physicochemical properties of VRP for percutaneous absorption and the well-recognized barrier function of the stratum corneum. Data obtained confirmed those reported previously using excised skin from hairless mice mounted in an *in vitro* permeation system (51) and guinea pig dorsal and human cadaver skins (51,52). Entrapment of VRP in polymethacrylate MPs significantly ($p<0.005$) reduced skin penetration to 5.6% (Fig. 10) with minimal skin permeation. This may be explained at least in part by *in vitro* release data, pointing to the reservoir action of MPs allowing relatively slow liberation of the drug to the gel vehicle and eventually the skin. A skin permeation retardant effect of microparticulate delivery systems was reported for the topical delivery of levothyroxine (53) and vitamin E (54). Inclusion of a skin penetration enhancer for free VRP would generate a composite system combining the advantages of polymer MPs as delivery system and promoting skin localization of a larger proportion of the drug. The effect of plain liposomes as skin penetration enhancers on diffusion of free VRP through the skin samples was investigated. Plain liposomes are used in community pharmacy practice as adjuvant in conventional dermatological preparations to modulate topical drug effects (55). Inclusion of commercially available plain liposomes in a physical blend with VRP (5% w/w) resulted in a considerably enhanced VRP skin localization (47.6%, Fig. 10) with minimal skin permeability through the full thickness skin. This can be attributed to reduced diffusion resistance of stratum corneum and gives support to the adjuvant topical use of liposomes. Skin-retained VRP was reported to be confined to the stratum corneum as dictated by its physicochemical properties (51). It is worth noting that the amount of VRP that permeated the full thickness human skin from the three test formulations did not exceed 1% at 24 h exposure time.

Based on these findings, a composite VRP gel with enhanced performance can be obtained by combining VRP polymer microparticles as controlled delivery system and plain liposomes as enhancer of skin penetration of the free drug. However, in-depth assessment of this approach, its applicability to different drugs and systems and its *in vivo* effects warrant further investigation.

CONCLUSION

Polymethacrylate MPs with required pharmaceutical attributes incorporating the hydrophilic drug VRP were formu-

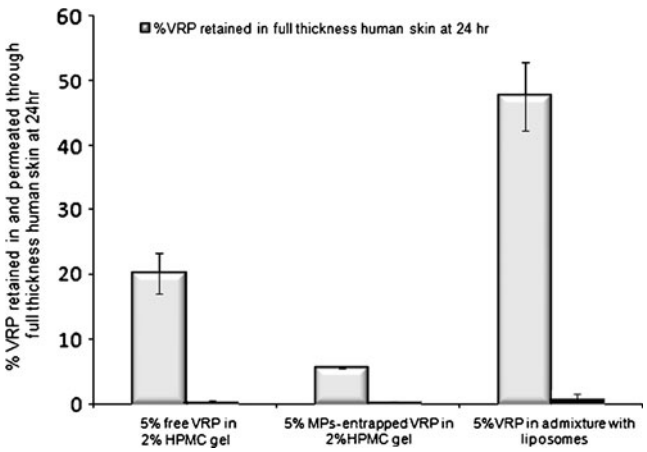

Fig. 10 Bar chart showing the *ex vivo* effect of formulation design on % VRP retained in or permeated through full-thickness human skin at 24 h. VRP concentration was 5%.

lated using an O/O emulsification solvent evaporation technique. Modulation of drug release from MPs could be achieved by controlling formulation variables including initial drug loading, composition of the polymethacrylate polymer matrix and HLB of the dispersing agent. The proportion of an interacting polymer component proved an important determinant of MP characteristics, particularly drug release. Involvement of factors known to influence drug release, such as MP size and high drug solubility, was outweighed by the strong drug-polymer interaction. A hybrid polymethacrylate MP VRP formulation with adequate pharmaceutical properties was used to prepare a gel for controlled topical delivery. *In vitro* drug release and *ex vivo* human skin permeability data provided evidence of controlled VRP delivery and skin localization with minimal skin permeation. A potential approach to enhance the performance of the composite VRP gel may be based on combining polymer MPs as a drug delivery system with a skin penetration enhancer for free VRP, plain liposomes in this study. Data obtained are a formulation approach to enhance the performance of topical VRP in response to the growing off-label topical use of calcium channel blockers by potentially minimizing systemic and cutaneous adverse effects.

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