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Basic Drug—Enterosoluble Polymer Coevaporates: Development of Oral Controlled Release Systems

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ABSTRACT

Precipitation of basic drugs within oral prolonged release systems, at the higher pH values of the intestine, would affect drug release. Coevaporates of a model basic drug verapamil HCl, in single or mixed polymer systems, containing Eudragit L100 (L100) and ethyl cellulose or Eudragit RS100, were prepared from ethanolic solution. XRD and DSC indicated loss of crystallinity of the drug in the coevaporates. The presence of the enterosoluble polymer in the system was found to aid in faster dissolution of the drug at higher pH values. This was affected by the presence and type of retarding polymer present in the system. Compression of the coevaporates resulted in either very slow release of the drug or undesirable changes in the release profile. Pelletization of a coevaporate containing drug and L100 yielded systems, which released the drug uniformly when studied by the buffer change method in simulated gastric (SGF) and intestinal (SIF) fluids. The presence of L100 in intimate contact with the drug was found to be essential for the desirable drug release properties of the system. The drug release occurred predominantly by diffusion in SGF and by a combination of diffusion and polymer dissolution/erosion in SIF. Appropriate choice of release modifiers and formulation variables and development of suitable formulations can yield systems which compensate for the reduced solubility of the drug in the higher pH environments of the intestine.

Key Words: Basic drug; Oral controlled release; Verapamil HCl; Eudragit L100; Coevaporates; Tablets; Pellets.

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INTRODUCTION

Precipitation of basic drugs at the higher pH values of the intestine, within oral prolonged release formulations, affects release rates and hence the bioavailability of the drug.[1] Various approaches have been employed to effect better release or achieve greater control over the release rates of such drugs from oral prolonged release systems.[2–14] The utility of solid dispersions of basic drugs in mixed polymer systems containing enterosoluble and insoluble polymers, in overcoming the problem of pH dependent solubility of the drug has been reported.[10–14]

Whereas some reports suggest that incorporation of the enteric coating polymer as a physical mixture with the basic drug in a formulation (consisting of other release retarding agents) can be used to obtain better release of the drug at higher pH values,[7–9] other reports have demonstrated the inability of the incorporated enteric polymer to provide pH-independent release.[4]

Two major mechanisms would be involved in the improved release of such basic drugs from systems containing enterosoluble polymers. 1) The dissolution of the polymer at higher pH values, would reduce the retarding nature of the system and enhance the release of the poorly soluble drug and 2) the formulation of such systems as solid dispersions, with the drug intimately dispersed in a matrix containing the enterosoluble polymer, would result in improved wetting and dissolution of the drug, and a possible solubilizing effect of the dissolving polymer, at the higher pH, thereby leading to better release of the poorly soluble drug. The first mechanism is expected to play a role irrespective of the method of incorporation of the polymer. The second however, would not play a major role in systems where the polymer has been incorporated in the system by means of simple physical mixing.

In either case, the ability of the enterosoluble polymer to dissolve from the system is a prerequisite for enhanced release of the basic drug in higher pH environments. The influence of other components of the system (e.g. release retarding polymers), and processing steps like compression would therefore significantly affect the release behavior and hence the performance of the system.

The use of Eudragit L100, in prolonged release coevaporates, to overcome the pH dependent solubility of model basic drug, verapamil HCl has been reported earlier.[9,11,13] The current study was aimed at investigating 1) the effect of method of incorporation of the polymer in the system 2) the influence of other components and formulation variables on the release of the drug and 3) the mechanisms of drug release from the coevaporate formulations.

MATERIALS AND METHODS

Materials

Verapamil HCl was obtained as a gift sample from Nicholas Piramal (I) Ltd. The Eudragit polymers (Röhm Pharma, GmbH) and ethyl cellulose 45 cps were donated by S. Zhaveri and Co., and Crown Chemicals, Mumbai respectively. All excipients used for preparation of tablets and pellets were obtained from Khandelwal Laboratories, Mumbai. All other materials used in the experiments were of analytical reagent grade.

Coevaporate Preparation

The coevaporation technique, ethanol as solvent and a coevaporation temperature not exceeding 50°C were employed to obtain the coevaporates of verapamil HCl.[15] The carriers used were ethyl cellulose 45 cps, Eudragit L100 (L100) and Eudragit RS100 (RS100). The coevaporates obtained were passed through sieve No 30 (pore size—500 μm) and the granules so obtained were stored in desiccators over anhydrous calcium chloride, at room temperature. The compositions and the codes of the coevaporates are listed in Table 1. The letters V, L, RS and EC in the codes are used to indicate presence of drug, L100, RS100 and ethyl cellulose in the coevaporate and the number at the end denotes different proportions of the components.

Table 1. Composition of coevaporates.

	Parts by weight			
Coevaporate	Verapamil HCl	Eudragit RS100	Eudragit L100	Ethyl cellulose, 45cps
VL[13]	1	0	1	0
VL1	1	0	0.75	0
VEC[13]	1	0	0	1
VRS	1	1	0	0
VECL[13]	1	0	0.69	1.06
VRSL1	1	1	1	0
VRSL2	1	0.5	1	0
VRSL3	1	0.65	1.3	0

The coevaporates were prepared with ethanol as solvent and evaporation temperatures not exceeding 50°C.

Physical mixtures were prepared by mixing the components in the same proportion as the coevaporates, and are coded similarly with the letters PM added at the beginning of the code.

Coevaporate Characterization

The infrared spectra of the samples were recorded on a Jasco FT/IR 5300 spectrophotometer. The DSC heating curves were recorded by heating the samples in open aluminum pans from 30°C to 300°C at 10°C per min, under a nitrogen flow of 50 ml/min in a Shimadzu DT-40 Thermal Analyzer. Powder X-ray diffraction patterns of all the solid dispersions, between 5 to 40° 2θ, were recorded using a Phillips X-ray diffractometer (Model—PW1820), using Cu K_α radiation (voltage 45 KV, current 30 mA), at a scanning rate of 2° 2θ per min.

Assay of Coevaporates

The coevaporates VL and VL1 were assayed by dissolving in simulated intestinal fluid, without pancreatin (SIF, prepared as per USP 23 and adjusted to pH 7.5±0.05).[16] The soluble polymer did not interfere with the spectrophotometric analysis of the drug at 278 nm. Other coevaporates, containing release-retarding polymer, were ground in a mortar to obtain fine powder. The drug from weighed amount of this powder was extracted in simulated gastric fluid without pepsin (SGF, prepared as per USP 23 and adjusted to pH 1.2±0.05)[16] and was analyzed spectrophotometrically at 278 nm for drug content.

Preparation of Tablets

Tablets of the coevaporates VECL, VL and VL1 were prepared by direct compression. The formulae used for the preparation of the tablets are given in Table 2. The tablets are coded similar to the coevaporates with the letter T after the code of the coevaporate and a number at the end to differentiate between different formulations (Table 2).

VECL and PMVECL tablets were compressed using 12.75 mm flat-faced punches and 11 mm flat-faced punches were used for VL, PMVL, VL-1 and PMVL-1 tablets. In addition, in order to qualitatively study the effect of compression of a physical mixture of an enteric polymer with the basic drug, PMVLT0 tablets were prepared by compression of PMVL lubricated with 0.5% of talc, using 9 mm standard concave punches.

The amounts of coevaporate (or physical mixture) used in the tableting experiments were equivalent to

Table 2. Formulae for tablets of verapamil HCl coevaporates.

	Tablet code[a]							
Ingredient	VECLT1	VECLT2	VECLT3	VLT1	VLT2	VLT3	VL1T1	VL1T2
Coevaporate	VECL equivalent to 120 mg of verapamil HCl			VL equivalent to 120 mg of verapamil HCl			VL1 equivalent to 120 mg of verapamil HCl	
DCP[b]	–	–	–	–	–	100 mg	–	–
Lactose[c]	170 mg	170 mg	–	100 mg	–	–	100 mg	–
MCC[d]	–	–	170 mg	–	100 mg	–		100 mg
Croscarmellose Sodium	–	15 mg	–	–	–	–	–	–
Starch	–	–	–	5%	5%	5%	3%	3%
Talc	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%
Colloidal silica	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%
Tablet mass (mg)	510±10	525±10	510±10	360±10	360±10	360±10	330±5	330±5

The tablets were prepared by direct compression.

[a]Tablets of physical mixtures corresponding to the coevaporates were prepared and coded similar to the coevaporate tablets with the letters PM at the beginning of the code.

[b]Directly compressible grade of Dibasic calcium phosphate, DCP Engranules, Enar Chemie, Mumbai, India.

[c]Directly compressible lactose, DMV International.

[d]Microcrystalline Cellulose Avicel PH 102, FMC Corporation.

120 mg of verapamil hydrochloride per tablet and were determined based on the drug content of the coevaporates/physical mixtures. All the tablets were compressed to a constant hardness of 4 to 5 kg/cm^2 as measured on a Monsanto hardness tester.

Preparation of Pellets

Pellets containing coevaporate VL were prepared using microcrystalline cellulose. The coevaporate VL (20 gm), previously passed through BSS sieve No. 30, was mixed well with microcrystalline cellulose (10 gm). This mix was kneaded using 10% w/w starch paste till an extrudable mass was obtained, passed through BSS sieve No. 14 to obtain extrudates, and spheronized on a Fuji Paudal Q-230 Spheronizer, fitted with a friction plate of groove dimensions 1 mm $\times$ 1 mm $\times$ 1 mm, for 5 min at 950 rpm. The pellets were dried in a tray drier for 2 h at 60°C; different size fractions were segregated by sieve analysis and stored over anhydrous calcium chloride at room temperature. Pellets of physical mixture PMVL were prepared in a similar way using PMVL instead of VL. The major sieve fractions, having a mean pellet size of 1625 μm (fraction A) and 1050 μm (fraction B), were used for evaluation. The drug content of the pellets was analyzed spectrophotometrically.

Drug Release

The in vitro drug release from coevaporates (equivalent to 120 mg of verapamil HCl), from the tablets and pellets, was studied in a USP type I apparatus at 100 rpm and 37 ± 0.5°C. The dissolution media used were 900 ml of SGF for the first 2 h, followed by 900 ml of SIF for the rest of the study.

The dissolution profiles of ''as is'' verapamil HCl and drug release patterns from VECL, VL and from pellets of fraction A were also studied separately in 900 ml of each medium.

Accelerated Stability

VL pellet fractions A and B were stored at 25°C, 37°C and 45°C in desiccators over anhydrous calcium chloride (RH ~ 0%) and at 40°C and 75% RH conditions. The pellets were assayed for drug content and evaluated for drug release profiles over a period of 6 months.

RESULTS

Coevaporate Characterization

The characteristic N-H stretching vibrations of the protonated amine of verapamil HCl[17] were seen between 2800 cm^{-1} and 2300 cm^{-1} in the IR spectrum of the drug as well as the physical mixtures. The peaks at around 2542 cm^{-1} were absent in the IR spectra of all the coevaporates, indicating a possible change in the nature of the protonated amine or interaction involving the protonated amine, in the coevaporates. The DSC heating curves of the physical mixtures exhibited the characteristic melting endotherm of the drug which was absent in the thermograms of all the coevaporates. The DSC curves of drug, PMVL and VL are shown in Fig. 1. The powder x-ray diffraction pattern of the drug and all physical mixtures exhibited sharp peaks,

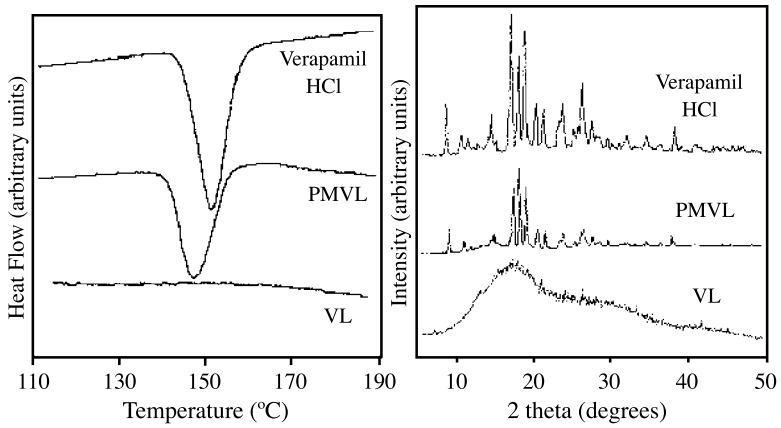

Figure 1. Physical characterization. Left panel shows the DSC heating curves of verapamil HCl, a representative coevaporate VL, and its corresponding physical mixture PMVL. Right panel shows their powder x-ray diffraction patterns.

indicating long range order in the drug phase. However the patterns of the coevaporates did not exhibit any peaks. These results indicate loss of crystallinity of the drug in the coevaporates (Fig. 1). During the process of coevaporation, the crystallization of the drug is inhibited. The drug therefore exists in an amorphous or molecularly dispersed form, intimately mixed with and entrapped in the polymeric matrix.

Assay of Coevaporates

The average drug content of the batches of VECL, VL and VL1 were 35% w/w, 49% w/w and 56% w/w respectively, which agreed well with the theoretical content.

Drug Release

'As Is' Drug

The aqueous solubility of Verapamil HCl drops from 82 mg/ml at pH 2.32 to 0.44 mg/ml at a pH of 7.32.[17] The 'as is' drug powder, passed through sieve # 60 (opening size 250 μm) was evaluated, to study the effect of medium pH on its dissolution rate, in SGF and SIF. The drug possesses higher solubility in SGF (pH 1.2) and hence dissolved rapidly and completely in 10 minutes. In SIF (pH 7.5), due to much lower drug solubility, the dissolution rate was lower. An average amount of around 73% dissolved in the first 10 minutes in SIF and the remaining amount dissolved slowly over a period of 2 h (Fig. 2).

Due to the low solubility of the drug in SIF, this medium would not provide perfect sink conditions for study of drug release from coevaporates and formulations. However, it would provide better discrimination between various sustained release systems, with respect to their ability to aid in improved dissolution of the drug at higher pH values. Hence, SIF (pH 7.5), which is the official dissolution test medium for Extended release Verapamil HCl tablets USP (USP23 1995), was used in the drug release studies.

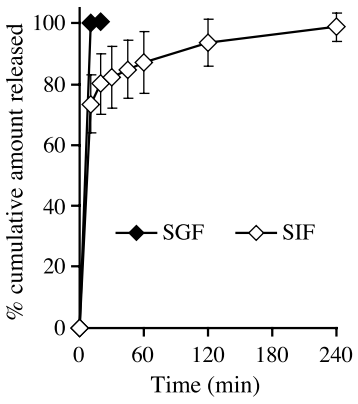

Figure 2. Dissolution profiles of plain verapamil HCl powder passed thro sieve # 60 (opening size 250 μm). The dissolution medium used was 900 ml of either SGF or SIF. Each data point is a mean of 3 determinations.

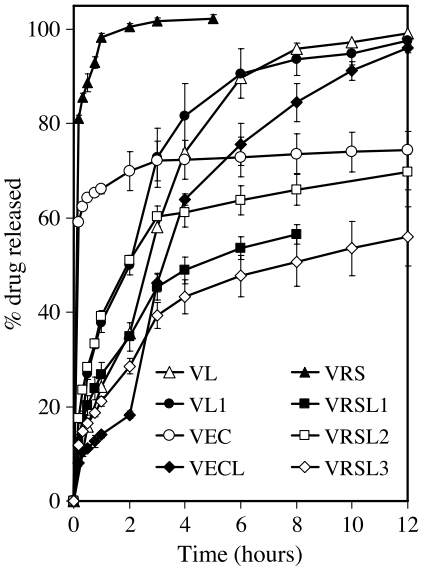

Figure 3. Release of verapamil HCl from solid dispersions, studied by buffer change method. The dissolution media used were SGF for the first 2 h followed by SIF for the rest of the study. Each data point is a mean of 6 determinations.

Coevaporates

The release profiles from coevaporates, studied by the buffer change method, are shown in Fig. 3. VECL released 18% of the drug in the first 2 h in SGF and almost all the drug over a period of 12 h. The coevaporate VEC released the drug rapidly in the acidic medium (70% in 2 h, Fig. 3). After change of buffer to SIF however, there was very little drug release with only around 5% of the drug being released in the next 10 h. A comparison of the release profile of VECL with that of VEC (which shows almost complete cessation of release in SIF, Fig. 3) indicates that the presence of an enterosoluble polymer in the system aids in improved release of the drug at higher pH values, where the drug possesses lower solubility.

In case of VEC, SGF penetrates the porous matrix of ethyl cellulose and the drug being highly soluble diffuses out of the system after dissolving in the

medium. After change of medium, the drug precipitates within the system as the free base and this affects the release rate. In VECL, the retarding polymer ethyl cellulose as well as the enterosoluble polymer L100 are insoluble in SGF and retard the release of the drug. Under the higher pH conditions of SIF, L100 dissolves and promotes the release of the drug.[11,13] Ethyl cellulose being an inert polymer would exert its retarding effect on drug release in a pH independent fashion.

In case of VL and VL1, the gastroresistant polymer, L100, retarded the release of the drug in SGF to a greater extent as compared to VEC (Fig. 3). After change of buffer however, the entire amount of drug was released quickly due to dissolution of L100. The higher polymer: drug ratio in VL results in greater retardation of drug release as compared to VL1 (Fig. 3). VRS did not show much retardation of release of the highly water-soluble drug. Practically all the drug was released in the first two hours in SGF with 81 % being released in the first 10 min (Fig. 3).

All coevaporates consisting of drug, L100 and RS100 exhibited pH dependent release with a drastic reduction in the release rate after change of medium to SIF. VRSL1 which contained equal quantities of drug and each of the two polymers released around 35% of drug in 2 h in SGF. However the release of drug in SIF was extremely slow with the total amount released at the end of 8 h being only 57% (Fig. 3). Attempts to improve release in SIF by increasing the proportion of L100 in the polymer system (VRSL2 and SVRSL3) were unsuccessful (Fig. 3). Further reduction of RS100 and increase in amount of L100 to obtain a Verapamil HCl: RS100: L100 ratio of 34:11:55, also did not result in better release of the drug in SIF. (Although the reasons for it could not be conclusively established, the drug release from this dispersion also exhibited large variations; data not shown).

A possible explanation for this behavior of RS100 containing systems (as compared to ethyl cellulose-based systems) is the inability of RS100 coevaporates to allow rapid dissolution of L100 at higher pH values. Here the drug gets converted to its poorly soluble weak base form, which is a viscous liquid. Also there is swelling of RS100. The inability of L100 to dissolve from the system possibly due to polymer – polymer interactions or due to its presence in a swollen intermingled polymer matrix could be the reason for slower release of the drug in SIF.

The release of drug from the coevaporates VECL and VL was also studied separately in SGF and SIF (Fig. 4). VECL released only 35% of the drug in 12 h in SGF and was more retarding than VL, which released 65% in 12 h. In SIF, the release of drug was faster from both the coevaporates, with 90% being released from VL within 6 h and around 88% from VECL in 12 h. Thus, greater retardation of release was seen in SGF as compared to SIF despite the greater solubility of the drug in SGF. This is because both the polymers are insoluble in SGF. In SIF, L100 dissolves from both VECL and VL, and aids in release of the drug. The release of drug from VL in SIF was much faster due to the fact that the only carrier present in the system was soluble in the medium. In case of VECL, in addition to the fact that the polymer content of the system was higher, the presence of ethyl cellulose, (which would exert a retarding effect on the release of drug and also on the dissolution of L100) resulted in slower release.

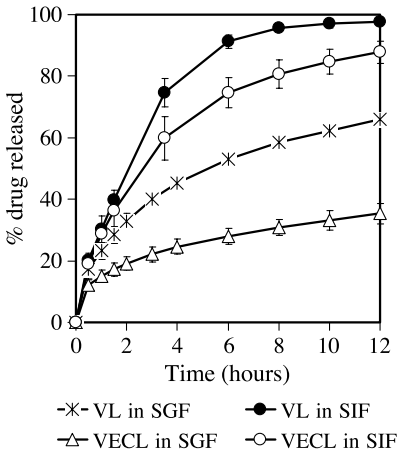

Figure 4. Release of verapamil HCl from coevaporates VL and VECL studied separately in SGF and SIF. Each data point is a mean of 3 determinations.

Tablets

The experiments on compression of the coevaporates were undertaken in order to study the effect of compression on the release properties and also to study the possibility of development of tablets for controlled release of the drug. Compression could be used as a means of retarding the release of the drug, from coevaporates based on L100 alone. The quantity of coevaporate used in the preparation of the tablets was based on the drug content of the dispersion batch used for the preparation of the tablets (Table 2). The amount of VECL, VL and VL1 used in the preparation of the powder mixtures for compression were ~340 mg, ~245 mg and ~215 mg per tablet respectively. The

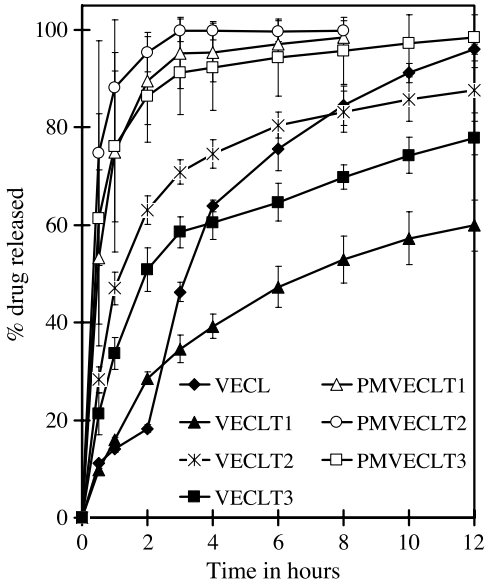

Figure 5. Release of verapamil HCl from VECL and PMVECL tablets. The dissolution media used were SGF for the first 2 h and SIF for the rest of the study. (n=3 for physical mixture systems and n=6 for coevaprate systems).

range of tablet weights for each formula is listed in Table 2. The tablets used in the dissolution study were weighed and the % drug release values were corrected for the individual tablet weights.

VECL tablets: Contrary to expectations, all tablets containing VECL, released greater amount of drug in SGF than the dispersion itself (18%). The extent of release in SGF was dependent on composition of the tablets. The release of the drug occurs by penetration of medium into the tablet, dissolution of the drug and its diffusion into the bulk of the medium, and by erosion of the tablet to expose more surface area for release. Excipients which promoted greater uptake of medium into the tablet (MCC) and erosion of the tablet (croscarmellose sodium) resulted in greater release of the drug in SGF (VECLT2 and VECLT3, Fig. 5).

After change of buffer to SIF, all the tablets released drug at a slow rate, with only 25% to 30% additional drug released in the next 10 h (Fig. 5). This was also contrary to what was seen for the coevaporate itself, which aids in improved and greater release of the drug in SIF. This indicated that the retarding effect of the system in SGF as well as the solubilizing effect of the enterosoluble polymer in SIF were lost as a consequence of compression of the coevaporate. A simultaneous loss of both the release attributes of the system, which seem to depend primarily on the association of the drug with the enterosoluble polymer, may indicate an adverse effect of compressive force on this association in the coevaporate, and needs further investigation.

Compressed physical mixtures were incapable of retarding the release of the drug in SGF (Fig. 5).

VL and VL1 tablets: Preliminary studies on compression of VL with directly compressible excipients, without any disintegrants, yielded tablets, which released the drug at a very slow rate (data not shown). The addition of starch in the tablets increased the amount of drug released and the directly compressible excipient used in the formulation affected the release profile. Only 27–65% of the drug was released from different tablet formulations of VL at the end of 12 h (Fig. 6). Lower proportion of polymer in VL1 resulted in around 75–80% release from VL1 tablets in 12 h (Fig. 6).

All the tablets of physical mixtures PMVL and PMVL1 except PMVLT0 however released almost all the drug within the first two hours (Fig. 6).

The coevaporates VL and VL1, when studied for drug release by the buffer change method, retarded drug release in SGF followed by very rapid release after change of medium. In case of the tablets made by compression of coevaporate VL, the release rate decreases perceptibly after a change in the medium. In case of tablets containing VL1, a more evident reduction in the release rate was observed after change

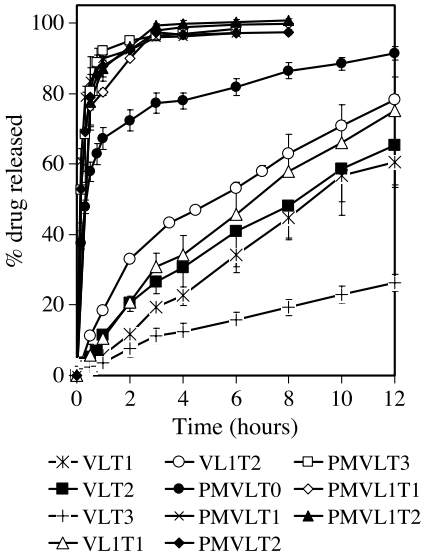

Figure 6. Release of verapamil HCl from VL, PMVL, VL1 and PMVL1 tablets. The dissolution media used were SGF for the first 2 h and SIF for the rest of the study. Error bars for some of the data sets are shown only on one side. (n=3 for physical mixture systems and n=6 for coevaprate systems).

of medium. This decrease in the slope of the dissolution curve after the change in medium might again indicate an adverse effect of compression on the association of the drug with the polymer. However, the overall retarding effect of compression is much higher. Hence, the effect of compression on the desirable release properties of the coevaporate although seen as the slight change in slope, is to a great extent masked by the retarding effect of compression.

As seen for VECL tablets, the release rate was highest from tablets containing MCC (VLT2 and VL1T2). In case of VLT3 tablets, presence of DCP, (which is an insoluble, non swelling, inert excipient in SIF) retards not only the release of the drug, but also the dissolution of L100, resulting in extremely low amounts of drug released (27% at the end of 12 h, Fig. 6). In comparison, VLT1 and VL1T1 tablets which contained lactose, released at a faster rate. Lactose being water soluble would dissolve and result in increased porosity of the tablet matrix, leading to better release in both the media.

As seen in Fig. 6, all the physical mixture tablets except PMVLT0 released almost all the drug in the first 2 h, in SGF. Presence of a directly compressible diluent promotes medium penetration (which is greater in case of hydrophilic diluents) and hence aids in drug release. PMVLT0 tablets were composed of the gastroresistant polymer-drug mixture and did not contain any diluent. The release of the drug in SGF was therefore retarded to a greater extent. Around 72% of the drug was released in 2 h in SGF; the remaining amount of drug was slowly and incompletely released over the next 10 h in SIF (Fig. 6).

Pellets

In order to retain the desirable release properties of VL and to exclude the highly retarding effects of compression, the coevaporate was pelletized as described. The drug content of the pellets was between 30% w/w to 33% w/w for all the sieve fractions, of all the batches of pellets prepared.

Release of drug from VL pellets was found to be uniform over a period of 12 h, Fraction A releasing 86% and Fraction B releasing the entire amount of drug in 12 h. There was good retardation of release of the water soluble form in SGF and enhanced release of the poorly soluble free base, after change of buffer to SIF (Fig. 7). The smaller mean pellet size in case of Fraction B resulted in greater surface area for drug release as well as shorter diffusion paths for release from the interior of the pellets. This resulted in higher amounts of drug released from pellets of Fraction B.

However the pellets made from PMVL showed highly pH dependent release with extremely slow release after change of buffer (Fig. 7a). The release in SGF was high with around 80% of the drug released from fraction A and 67% from fraction B, in 2 h. Upon change of buffer, the remaining amount of drug was released extremely slowly, with fraction B pellets releasing the remaining drug only in the next 10 h and fraction A pellets releasing a cumulative amount of 90% in a total of 12 h.

Drug release from tablets and pellets of physical mixtures, indicates that the existence of the drug as an

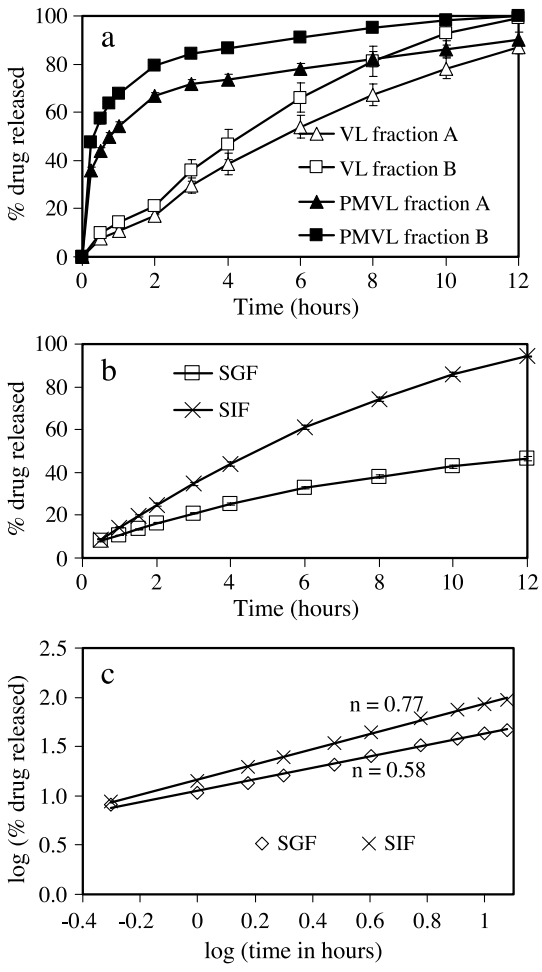

Figure 7. (a) Release of verapamil HCl from VL and PMVL pellets of size fraction A and B. The dissolution media used were SGF for the first 2 h and SIF for the rest of the study. (n=3 for physical mixture systems and n=6 for coevaprate systems). (b) Release of verapamil HCl from VL pellets, Fraction A, studied separately in SGF and SIF. Each data point is a mean of 6 determinations. (c) Double logarithmic plots for the release of drug from VL pellets, Fraction A in SGF and SIF.

intimate mixture with the polymer (as in a coevaporate system) is essential for effective retardation of drug release in SGF and also vital for the solubilizing and release promoting effect of the polymer in SIF. Hence, the mechanism of enhanced drug release in SIF is not based only on polymer dissolution, leading to increased porosity of the system (as this effect is not seen in case of physical mixture pellets), but may also involve improved wetting and increased drug surface area made available by the coevaporate system and a solubilizing effect of the dissolving polymer exerted in the microenvironment surrounding the drug. It is however understood that this may be not be strictly true for all such systems and will depend on the drug and system under consideration.

Pellets of fraction A were studied for drug release separately in SGF and SIF (Fig. 7b). The release in SGF was slow with only about 46% of the drug released in 12 h, whereas in SIF, 94% of the drug was released in 12 h. In order to study the release mechanisms in the two media, the release data was fit into the empirical power law equation,[18,19] which can be mathematically transformed as follows.

$$\log(\%\ \text{drug released at time t}) = 2 + \log k + n \log t \quad (1)$$

A plot of log (% cumulative release) v/s log (time) yields a line with slope 'n'. The value of 'n' indicates mechanism of release. For both swellable and non-swellable spherical devices a value of 'n' equal to 0.43 would indicate Fickian release based on drug diffusion. Greater values of n (between 0.43 and 0.85, for swellable spherical devices and between 0.43 and 1.0 for non-swellable spherical devices) would indicate lesser contribution of diffusion, and anomalous release based on a combination of different release mechanisms. Since the release from the pellets in SIF would be influenced by swelling of the pellet mass, pore diffusion of the drug as well as dissolution of the polymer, the release would occur by a combination of various mechanisms. The value of the slope was used to derive qualitative information about the release mechanism in the different media.

The slopes of the double logarithmic plots (Fig. 7c) were 0.58 and 0.77 for the release profiles in SGF and SIF respectively. This indicates predominantly diffusion-controlled release in SGF. The drug being highly soluble in SGF, would dissolve in the invading acidic fluids and diffuse out through the porous polymeric network of the coevaporate particles and the aqueous channels in the pellet mass. The swelling of the MCC based pellet due to water imbibition and erosion of the pellet could also contribute to the release. In SIF, the drug has poor solubility and diffusional release is significantly reduced. However since the polymer is soluble, the dissolution/erosion of the enterosoluble matrix contributes to drug release (higher value of 'n'). Since diffusion of the poorly soluble species would also contribute to the overall release in SIF, the release would be a combination of the two mechanisms, which is reflected in the value of the slope.

The profiles also indicate a dependence of the release of drug, at higher pH values, on dissolution of L100. The release of the drug is extremely slow in SGF due to the presence of the gastroresistant polymer entrapping the drug, despite the drug being in its highly soluble form. Although the drug exists in its free base form in SIF, where diffusion contribution to overall release is expected to be low, due to poor solubility of the drug, the release of the drug is much higher than that in SGF. This is due to the much faster dissolution/erosion based release of the drug, due to the presence of L100.

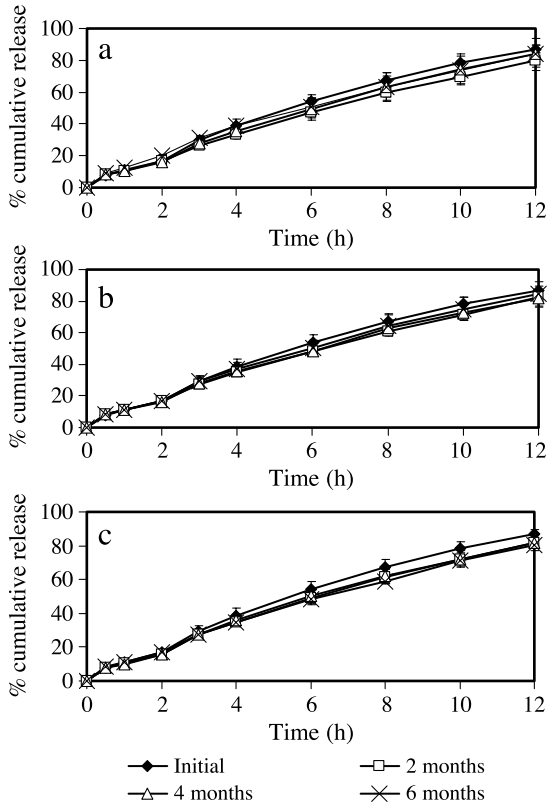

Figure 8. Drug release profiles from VL pellets (Fraction A) stored at (a) 37°C, (b) 45°C and (c) 40°C/70% RH conditions. Each data point is a mean of 3 determinations.

Accelerated Stability

Since coevaporates are based on amorphous or metastable forms of the drug, there is a tendency for the drug to convert to the stable form on storage. Humidity and temperature, by accelerating this conversion, can affect the release characteristics of the formulation. The release profiles from the pellets were however unaffected by exposure to accelerated conditions of temperature and humidity over a period of 6 months. Fig. 8 shows the drug release profiles from VL pellets, Fraction A, stored under accelerated stability conditions.

CONCLUSIONS

Enterosoluble polymers can be used in oral controlled release formulations to overcome the problem of pH dependent solubility of weakly basic drugs. Intimate mixture of the drug with the enterosoluble polymer seems to be a requirement for improved dissolution of the drug from the system at higher pH values. Compression of solid dispersion systems to obtain tablets can cause undesirable changes in the drug release properties of these systems. However, appropriate choice of release modifiers and formulation variables and development of suitable formulations can yield systems with release characteristics that compensate for the reduced solubility of the drug in the higher pH environments of the intestine.

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