IJPSR (2017), Vol. 8, Issue 5 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 21 October, 2016; received in revised form, 27 December, 2016; accepted, 31 December, 2016; published 01 May, 2017

POLYMER COMBINATION FOR PARENTERAL DRUG DELIVERY

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Keywords:

Polymer Combination, Parenteral, Drug Delivery

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ABSTRACT: The number of medical applications for natural or synthetic biomaterials contin\ues to expand. One particularly interesting development concerns the use of injectable polymeric biomaterials. The forms in which the biomaterials are injected can vary from particulate matter, *e.g.*, microspheres or irregularly shaped particles, to gels and cements that are injected in liquid form and which harden inside the body. Polymers have played an integral role in the advancement of drug delivery technology by providing controlled release of therapeutic agents in constant doses over long periods, cyclic dosage, and tunable release of both hydrophilic and hydrophobic drugs. The development of using polymer combination have attracted much attention because the biodegradation rate of the copolymer is easily controlled by altering its composition. In this review, the fundamental drug delivery systems from polymer blends including the origins and applications of polymer blend systems and polymer blend therapeutics are highlighted. The PCL microparticle-dispersed PLGA solution may be a good candidate as an injectable bulking agent. Using PCL–PLGA blend, the porous structure of the polymer blends dependent on the blend ratio under the same conditions other than the ratio. When blending PLGA with PEG, the in vitro release studies showed that the initial burst effect was dependent on the PLGA/PEG blend ratio. Moreover, the release rate increased in direct relation to PEG content. Blending PCL with poly(methacrylate) showed that the greater the poly(methacrylate) content, the less pronounced the burst effect and the more sustained the release effect. The latest developments in polymer blend capable of molecular recognition or directing intracellular delivery are surveyed to illustrate areas of research advancing the frontiers of drug delivery.

INTRODUCTION: The parenteral administration route is the most effective and common form of delivery for active drug substances with metabolic bio-availabilities drug for which the bio-availability is limited by high first pass metabolism effect or other physicochemical limitation and for drugs with a narrow therapeutic index.

QUICK RESPONSE CODE

DOI:
10.13040/IJPSR.0975-8232.8(5).1993-02

Article can be accessed online on:
www.ijpsr.com

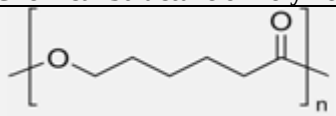
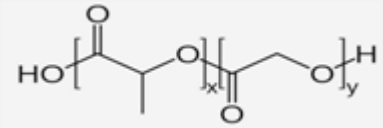
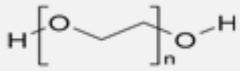
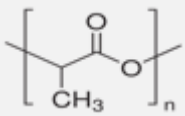
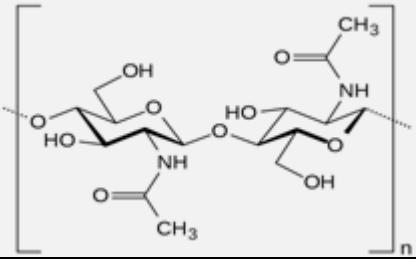
DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.8 (5).1993-02

For this reason, whatever drug delivery technology that can reduce the total number of injection throughout the drug therapy period will be truly advantageous not only in terms of compliance, but also for potential to improve the quality of the therapy. Such reduction in frequency of drug dosing is achieved, in practice, by the use of specific formulation technologies that guarantee that the release of the active drug substance happens in a slow and predictable manner. For several drugs, depending on the dose, it may be possible to reduce the injection frequency from daily to once or twice monthly or even less frequently.

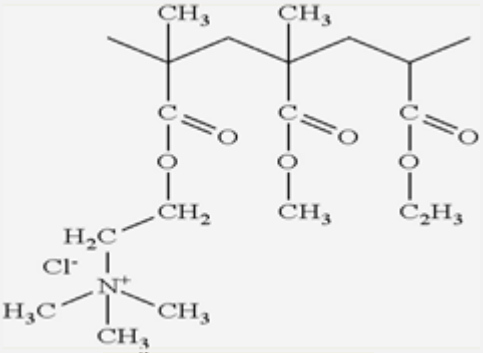
In addition to improve patient comfort, less frequent injection of drugs in the form of depot formulation smoothes out the plasma concentration time profiles by eliminating the peaks and valleys. Such smoothing out of the plasma profiles has the potential to not only boost the therapeutic benefit but also to reduce unwanted side effects. The release can either be continuous or pulsatile depending on the structure of the device and the polymer characteristics, continuous release profiles are suitable to generate on infusion like plasma level time profile in the systemic circulation without the necessity of hospitalization.

Biodegradable Polymers in Controlled Release Drug Delivery: A range of materials have been employed to control the release of drugs and other active agents. The earliest of these polymers were originally intended for other, nonbiological uses, and were selected because of their desirable physical properties. To be successfully used in controlled drug delivery formulations, a material must be chemically inert and free of leachable impurities. It must also have an appropriate physical structure, with minimal undesired aging, and be readily processable. Some of the materials that are currently being used or studied for controlled drug delivery include (Poly(methyl methacrylate). However, in recent years additional polymers designed primarily for medical applications have entered the arena of controlled release. Many of these materials are designed to degrade within the body (Poly(lactide-co-glycolides) (PLGA)). Originally, polylactides and polyglycolides were used as absorbable suture material, and it was a natural step to work with these polymers in controlled drug delivery systems. The greatest advantage of these degradable polymers is that they are broken down into biologically acceptable molecules that are metabolized and removed from the body via normal metabolic pathways. However, biodegradable materials do produce degradation by-products that must be tolerated with little or no adverse reactions within the biological environment. Generally, biodegradable polymers used for the preparation of parenteral controlled drug delivery system will be degraded in and hence does not require removal from the body. Biodegradable polymers investigated for controlled drug delivery are polylactide/polyglycolide polymers, polycaprolactone, polyorthoesters, natural polymers etc. Biodegradable polymer used as pharmaceutical excipient showed in **Table 1**.

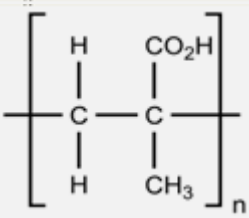
TABLE 1: BIODEGRADABLE POLYMERS

Type of Polymer	Chemical Structure of Polymer
Polycaprolactone	
Poly(DL-lactic-co-glycolic acid) (PLGA)	
Poly(ethylene glycol)	
Poly(L-lactic acid)	
Chitin	

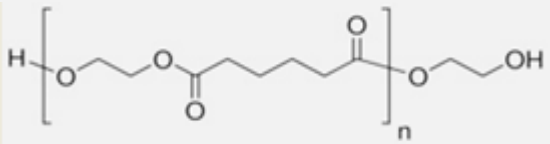
Eudragit® RS 100



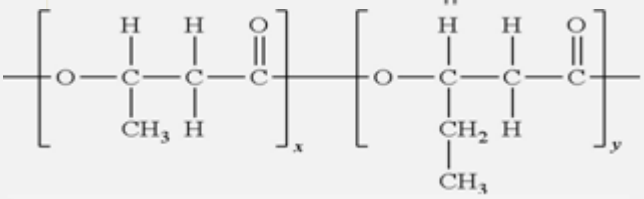
Poly(methacrylate)



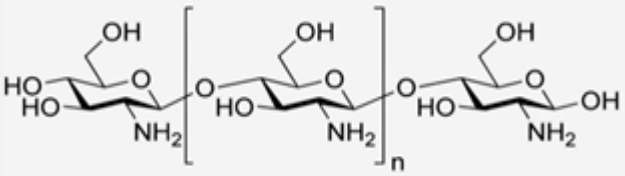
Poly(ethylene adipate)



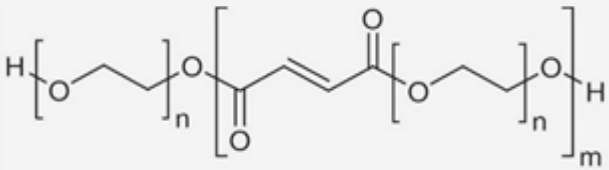
Poly(hydroxyl butyrate-hydroxyvalerate)



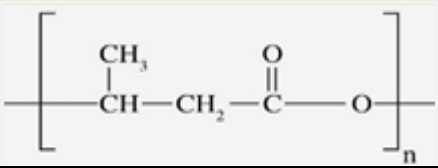
Chitosan



Polyethylene glycol fumarate



Poly-(3-hydroxybutyrate)



PLA is a synthetic biodegradable polymer, thus PEG-PLA copolymers have been widely used in drug delivery. The recent advances of these copolymers have been reviewed by Zeng *et al.*,[1]. These studies have proven the practical utility of polymer self-assemblies as injectable nano-drug delivery systems through both experimental and clinical results, which has generated much interest because they provide a strong foundation for further development in the nano-DDS field.

Ortiz *et al.*,[2] have engineered two 5-fluorouracil-loaded nanoparticulate systems based on the biodegradable polymers poly(butylcyanoacrylate) and poly(ε-caprolactone). Drug incorporation to the nanosystems was accomplished by entrapment (encapsulation/dispersion) within the polymeric network during nanoparticle synthesis, *i.e.*, by anionic polymerization of the monomer and interfacial polymer disposition, respectively. Main factors determining 5-fluorouracil incorporation within the polymeric nanomatrices were

investigated. These nanocarriers were characterized by high drug entrapment efficiencies and sustained drug-release profiles. *In vitro* studies using human and murine colon cancer cell lines demonstrated that both types of nanocarriers significantly increased the antiproliferative effect of the encapsulated drug.

Polymer Combination for parenteral drug delivery: Most of formulations using biodegradable polymer has become a well-established technology for controlled release drug delivery. The development of using polymer combination have attracted much attention because the biodegradation rate of the copolymer is easily controlled by altering its composition. Many works has been reported regarding this issue.[3, 4, 5, 6] Potential injectable urethral bulking agent of PCL microparticle-dispersed PLGA solutions have been published by Heang Oh *et al*., [4]. The mixture solutions were prepared by mixing polycaprolactone (PCL) microparticles (diameter, 100-200 μm; fabricated by a temperature-induced phase transition method) and poly(DL-lactic-co-glycolic acid) (PLGA) solution (dissolved in tetraglycol to 10 wt%) with different PCL microparticle to PLGA solution ratio. The mixture solution was solidified by the precipitation of PLGA when the solution was contact with water.

In contact with water, the PCL microparticles exhibited a well-packed structure entrapped in a solidified porous PLGA matrix, which can effectively prevent the microparticle migration in the body and retain its initial volume even after PLGA matrix degradation. The PCL microparticle-dispersed PLGA solution may be a good candidate as an injectable bulking agent for the treatment of urinary incontinence owing to its good injectability, volume retention potential as well as biocompatibility. Other works has been conducted by Theerasilp and Nasongkla.[7]

Parenteral microparticles of poly (DL-lactic-co-glycolic acid) (PLGA) 50:50 and poly(ethylene glycol) (PEG) blends with entrapped model drug compounds to investigate the effect of blend ratio on release kinetics has been fabricated by Cleek *et al*., Two model drugs (FITC-IgG and FITC-dextran) were entrapped using a double-emulsion-solvent-extraction technique with high efficiency. In vitro release studies showed that the initial burst effect was dependent on the PLGA/PEG blend ratio. Moreover, the release rate increased in direct relation to PEG content for up to 28 days.

A linear release profile was obtained for microparticles loaded with FITC-IgG for initial PEG weight fractions. A biphasic release profile was obtained for FITC-dextran loaded microparticles with rates dependent on the PEG content as shown in **Fig 1**. These results demonstrate the feasibility of modulating the release profile of entrapped compounds in biodegradable microparticles by adjusting the PLGA/PEG blend ratio [5].

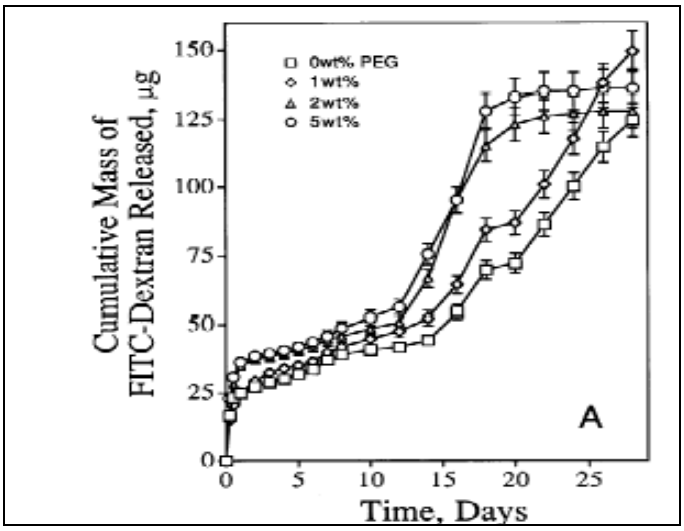


FIG. 1: BIPHASIC CUMULATIVE RELEASE OF DEXTRAN FROM FITC-DEXTRAN LOADED MICROPARTICLES [5]

Tanaka *et al*., (2008) have prepared microporous foams of polymer blends of two biodegradable polyesters, poly(L-lactic acid) (PLLA) and poly(ε-caprolactone) (PCL) via thermally induced phase separation method. The phase behaviors of the solutions of the polymer blends in 1,4-dioxane containing water were similar, which would be due to the similar solubility parameters of the two polymers.

However, the porous structure of the polymer blends dependent on the blend ratio under the same conditions other than the ratio. Hepatic cells (HepG2 cells) were cultured on the porous polymer blends. The cells invaded into the scaffold of PCL and PLLA–PCL-blend (1:4) by 1.0 and 1.5 mm, respectively, while they grew near the surface of the PLLA foams. Blending of biodegradable

polyesters has the potential of controlling the porous structure of biodegradable foams [6].

Formulations of the blends for controllable release of bovine serum albumin (BSA) which are based on the balance among the hydration rate of the chitin phase and degradation of chitin/PLA and PLGA phase developed by Long Mi *et al*., (2003) [8]. These biodegradable microspheres were prepared by polymers blending and wet phase-inversion methods. The parameters such as selected non-solvents, temperature of water and ratio of polylactide to polyglycolide were adjusted to improve thermodynamic compatibility of individual polymer (chitin and PLGAs or chitin/ PLA), which affects the hydration and degradation properties of the blend microspheres. Triphasic pattern of drug release model is observed from the release of protein from the chitin/PLGAs and chitin/PLA microspheres: the initially fast release (the first phase), the following slow release (the second phase) and the second burst release (the third phase). A chitin/PLGA 50/50 microsphere is novel and interesting, and may be used as a protein delivery system.

Graves *et al*., (2004) have used two different PLGA samples (Resomer 502 and Resomer 506), either alone or in combinations to prepare microcapsules. Microcapsules were prepared using a double emulsion solvent evaporation technique [9]. The efficiency of encapsulation increased significantly when a mixture of 1 part Resomer 506 and 7 parts Resomer 502 was used to prepare the microcapsules. In contrast, irrespective of the relative ratio of Resomer 502/Resomer 506, the median particle size of the microcapsules showed similar distribution pattern. The glass transition temperature (Tg) decreased significantly as the amount of Resomer 502 was increased in the formulation. The presence of Resomer 502 at lower concentration, along with Resomer 506, initially reduced the burst effect. However, incorporation of a higher amount of Resomer 502 increased the burst effect. Drug release from these microcapsules continued over 80 days. The presence of a larger amount of polymer was expected to reduce the burst release by forming a dense polymer coating on the surface of the microcapsules. However, these formulations contain either a very low amount or none at all, of the high *M*w PLGA. Thus, use of low *M*w PLGA may have increased the diffusion of pentamidine (**Fig. 2)**. Efficiency of encapsulation increased significantly when Resomer 506 was mixed with Resomer 502 at a ratio of 1:7. Blending of Resomer 502 with Resomer 506 reduced the glass transition temperature, which resulted in higher amount of drug release [9].

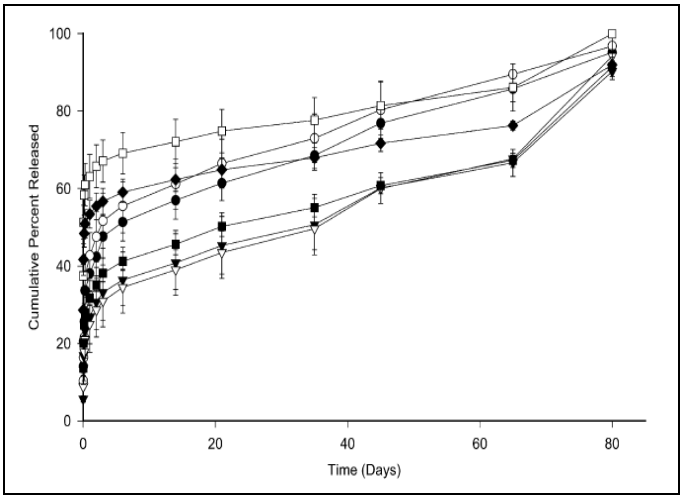


FIG. 2: DISSOLUTION PROFILE OF MICROCAPSULES WITH DIFFERENT RATIO OF PLGA RESOMERS [9]

Poly lactic-co-glycolic acid nanoparticles (PLGA-NP) have been extensively studied for vaccine delivery and have been reported to target dendritic cells naturally through phagocytosis with efficient delivery of the vaccine components. PLGA-NP can accommodate a wide range of actives and in the present study were loaded with the model vaccine antigen ovalbumin and the adjuvants monophosphoryl lipid A (MPL) and Quil A (QA) before being combined with thermoresponsive hydrogels with the aim of creating a oneshot vaccine. [10] Another study regarding injectable implant for intratumoral delivery has been conducted and evaluated as injectable dosage forms [11]. The incorporation of the poly(methacrylate) which enabled the fine tuning of the particle size and the release kinetics; was developed by the encapsulation of the antiretroviral efavirenz (EFV) within pure PCL, pure Eudragit® RS 100 and PCL/Eudragit® RS 100 and of blend particles using two different methods (nanoprecipitation and emulsion/solvent diffusion/evaporation). Results showed that the greater the poly(methacrylate) content, the less pronounced the burst effect and the more sustained the release [12].

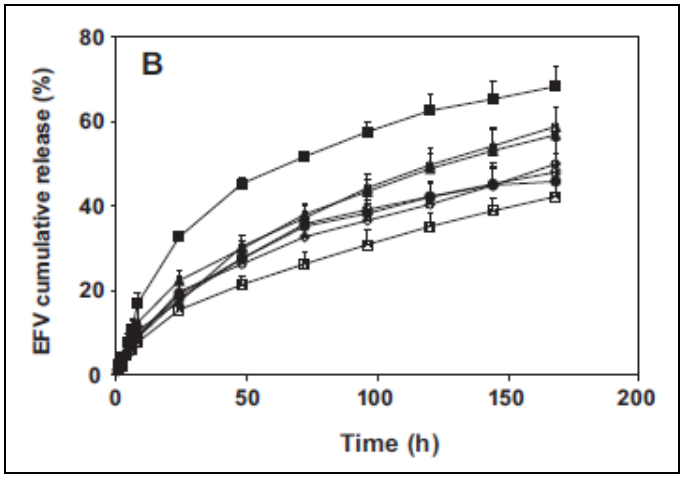


FIG. 3: EFV CUMULATIVE RELEASE FROM DIFFERENT DRUG-LOADED PARTICLES PREPARED BY THE NANOPRECIPITATION AND THE EMULSION TECHNIQUE OVER (A) 24 H AND (B) 168 H [12]

Regardless of the polymer composition and the production technique, all the systems displayed remarkably high encapsulation efficiency and drug payload. On the other hand, nanoprecipitation resulted in smaller particles and narrower size distribution patterns. These data together with the greater simplicity, reproducibility and eventually scalability in an industrial setup, make this method more advantageous than the traditional emulsion one.

Spherical reservoir-type microcapsules composed of poly(ethylene adipate) (PEAD) and 20% poly-scaprolactone (PCL II), poly(hydroxyl butyrate-hydroxyvalerate) (P(HB-HV)); 10.8% HV) 20% PCL II and a blend of P(HB-HV)/PEAD 20% PCL II containing bovine serum albumin (BSA; surrogate protein)-loaded agarose have been fabricated using a double emulsion technique with solvent evaporation by Atkins (1997) [13]. P(HB-HV) and PEAD microcapsules had microporous and smooth surfaces. Irrespective of the fabrication polymer, microcapsules were generated in high yield (>75%) and BSA incorporation had no significant effect on microcapsule size distribution (8-200 µm). The loss of BSA, both by partitioning into aqueous continuous phase and through the micropores of P(HB-HV) microcapsules as BSA-loaded agarose during the precipitation of the fabrication polymer concomitant with solvent evaporation, resulted in low encapsulation efficiencies (<15%). In all cases BSA release could be monitored for up to 26d and the amount and duration of BSA release from P(HB-HV) 20% PCL II microcapsules was influenced by micropore number and diameter, and by the extent of reservoir loading, while BSA release from smooth PEAD microcapsules was assumed to be the result of an increase in membrane porosity [13].

Bramfeldt and colleagues (2008) have recently reported binary blends which were prepared from poly(ε-caprolactone) (PCL), and P(CL-co-D,L-lactic acid)-P(ethylene glycol)-P(CL-co-D,L-lactic acid) co-polymers, where the D,L-LA content in the side chains varied from 0 to 70 mol% [14]. Blend discs were fabricated by melt-molding, and the effect of blend composition on hydrolytic degradation was studied. Variations in medium pH were monitored, and morphological changes were observed using scanning electron microscopy. Blending of these co-polymers was found to constitute a simple means by which intermediate rates of water absorption and mass loss were obtained, compared to those observed in pure co-polymer preparations. In one of the blends, prepared from the two components containing 70 or 0 mol% D,L-LA in the side chains and thereby exhibiting large differences in degradation rate, hydrolysis resulted in the formation of a porous material over time. Furthermore, all blend samples maintained their initial shape throughout the study. Such materials may be interesting for further investigations for applications in cellular therapy and controlled release [14, 15, 16].

Doulabia *et al.*, (2013) have prepared chitosan/polyethylene glycol fumarate (chitosan/ PEGF) blend films as wound dressings and to evaluate the influence of composition ratio on the blending properties of the films [17]. Blending chitosan with PEGF obviated the brittleness of neat chitosan film. Film topography performed by atomic force microscopy illustrated that blending could increase and control the surface roughness of the neat film. Controlled water solubility, swelling, wettability and surface tension of the blend films were also evaluated. Physical properties as well as antibacterial activity assessments showed that among different compositions, the film comprising 80 wt% chitosan and 20 wt% PEGF is a suitable candidate for biomedical applications as a wound dressing material.

Bovine serum albumin (BSA) as a model protein drug was encapsulated with a microparticle based on the blend of poly(D,L-lactic-co-glycolic acid) (PLGA) and poly(L-lactide)-g-oligo(ethylene glycol) (PLLA-g-oligoEG) by W/O/W double emulsion method [18]. Drug loading efficiency increased with increase in the graft frequency of oligo EG in the graft copolymer in the blend. The release of BSA was found to be more efficient for microparticles based on the blend than on the PLGA, which is due to the faster protein diffusion through the swollen phase of the hydrogel-like structure. The microparticles based on the blend showed a slower degradation and a lower pH shift compared to that of PLGA.

Poly - (3-hydroxybutyrate) (P(3HB)) is a biodegradable and biocompatible polymer that has been used to obtain polymer-based drug carriers. Bidone *et al*., (2009) used two strategies for prolonging ibuprofen (IBF) release from P(3HB)-based microspheres which were tested: blending with poly(D,L-lactide)-b-polyethylene glycol (mPEG-PLA); and obtaining composite particles with gelatin (GEL) [19]. IBF-loaded microspheres were prepared by an oil-in water (O/W) emulsion-solvent evaporation method. SEM micrographs showed particles that were spherical and had a rough surface. A slight decrease of the crystallinity degree of P(3HB) was observed only in the DSC thermogram obtained from unloaded-microspheres prepared from 1:1 P(3HB):mPEG-PLA blend. For IBF-loaded microspheres, a reduction of around 10 °C in the melting temperature of P(3HB) was observed, indicating that the crystalline structure of the polymer was affected in the presence of the drug. DSC studies also yielded evidence of the presence of a molecular dispersion coexisting with a crystalline dispersion in the drug in the matrix. Similar results were obtained from X-ray diffractograms.

In spite of 1:1 mPEG-PLA:P(3HB) blends having contributed to the reduction of the burst effect, a more controlled drug release was provided by the use of the 3:1 P(3HB):mPEGPLA blend. This result indicated that particle hydration played an important role in the drug release. On the other hand, the preparation of P(3HB):GEL composite microspheres did not allow control of the IBF release [19].

Blanco-Príeto *et al*., (2004) developed Vapreotide which was microencapsulated into end-group capped and uncapped low molecular weight poly(lactide) (PLA) and poly(lactide-coglycolide) (PLGA) by spray-drying and coacervation. Microspheres were prepared from single and blended (1:1) polymer types [20]. Spray-drying and coacervation produced microspheres in the size range of 1–15 and 10–70 µm, respectively, and with encapsulation efficiencies varying between 46% and 87%. In vitro release of vapreotide followed a regular pattern and lasted more than 4 weeks, time at which 40–80% of the total dose were released. Microspheres made of 14-kDa end-group uncapped PLGA50:50 or 1:1 blends of this polymer with 35 kDa end-group uncapped PLGA50:50 gave the best release profiles and yielded the most sustained plasma levels above a pre-defined 1 ng/ml over approximately 14 days.

In vitro/in vivo correlation analyses showed for several microsphere formulations a linear correlation between the mean residence time in vivo and the mean dissolution time ($r = 0.958$) and also between the amount released between 6 h and 14 days. For several other parameters or time periods, no in vitro/in vivo correlation was found. This study demonstrates that controlled release of the vapreotide is possible in vivo for a duration of a least 2 weeks when administered i.m. to rats. These results constitute a step forward towards a twice-a-month or once-a-month microsphere-formulation for the treatment of acromegaly and neuroendocrine tumors.

Paclitaxel-loaded biodegradable drug delivery systems manufactured from poly(lactic-*co*-glycolic acid) (PLGA) are known to release the drug at extremely slow rates. Jackson *et al*., (2007) investigated paclitaxel-loaded microspheres composed of blends of PLGA with low molecular weight ampipathic diblock copolymers by solvent evaporation method. The encapsulation and release of a series of poly(ε-caprolactone) (PCL)- or poly (d,l-lactic acid) (PDLLA)-*co*-methoxy polyethylene glycol (MePEG) diblock copolymers was measured using quantitative gel permeation chromatography [21]. The PCL- and PDLLA-based diblock copolymers encapsulated at high efficiency and were miscible in PLGA microspheres (30–120 µm size range). The burst phase of paclitaxel release

was increased up to 20-fold by the inclusion of diblock copolymers in PLGA microspheres. Approximately 10% of the more hydrophobic PCL-based copolymers released from the microspheres in a short burst over 3 days followed by very slow release over the following 10 weeks. Only the PDLLA-based copolymer released from the PLGA microspheres in a controlled manner over 10 weeks. All microspheres containing PEG were found to have more hydrophilic surfaces (as measured by contact angle) with improved biocompatibility (reduced neutrophil activation) compared to PLGA only microspheres. These results indicate that low molecular weight polyester-based diblock copolymers may be effectively encapsulated in PLGA microspheres to increase paclitaxel release (probably through a micellization process) and improve biocompatibility.

A poly(ethylene glycol)-blockpoly (ε-caprolactone) (PEG-b-PCL) micelles have been produced with carrying capacity for Paclitaxel (PTX), cyclopamine (CYP), and gossypol (GSP) A similar relative pattern of in vitro drug release for 3-drug PEG-b-PCL micelles was observed (**Fig. 4**). All three drugs were released from PEG-b-PCL micelles over 72 h in a biphasic pattern [22].

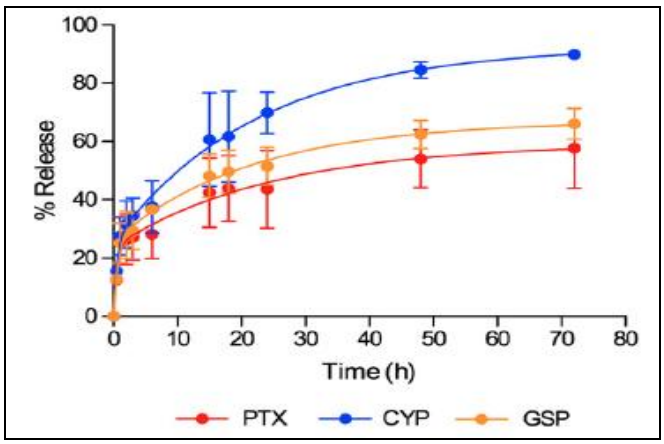


FIG. 4: *IN VITRO* DRUG RELEASE OF PACLITAXEL (PTX), CYCLOPAMINE (CYP), AND GOSSYPOL (GSP) FROM MICELLES PACLITAXEL (PTX), CYCLOPAMINE (CYP), AND GOSSYPOL (GSP) [22]

The influence of polymer interaction and distribution on drug release from microparticles fabricated from blends of pH dependent polymer (Eudragit S, soluble above pH 7) and pH independent polymer (Eudragit RL, Eudragit RS or ethylcellulose) incorporated into prednisolone loaded microparticles using a novel emulsion solvent evaporation method has been studied [23, 24].

Microparticles fabricated from blends of Eudragit S and Eudragit RL or RS did not modify drug release compared to microparticles fabricated from Eudragit S alone. This can be attributed to the high degree of miscibility of Eudragit S with Eudragit RS or Eudragit RL within the microparticles as confirmed by glass transition temperature measurements and confocal laser scanning microscopy.

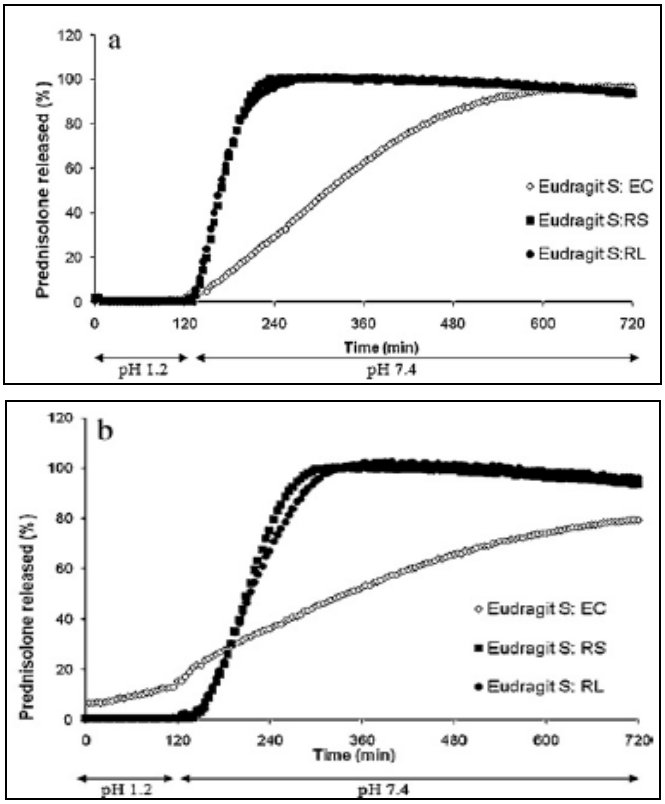


FIG. 5: *IN VITRO* RELEASE OF PREDNISOLONE FROM EUDRAGIT S: RS, EUDRAGIT S:RL AND EUDRAGIT S:ETHYLCELLULOSE (EC) BLEND MICROPARTICLES (A) 75:25, (B) 50:50 [23]

Study from Liu *et al.*, 2013 using Carbamazepine (CBZ) as model drug and combinations of Kollidon VA64 (VA64), Soluplus (SOL) and Eudragit EPO (EPO) as polymer utilized as carriers show that drug-polymer miscibility at temperatures below melting point (Tm) of CBZ was improved by combining EPO with VA64 or SOL. With 30% drug loading in a solid dispersion in SOL:EPO (1:1, w/w), CBZ was mainly present in an amorphous form accompanied by a small amount of a microcrystalline form. The dissolution rate of the solid dispersion was significantly increased

(approximately 90% within 5 min) compared to either the pure drug (approximately 85% within 60 min) or the corresponding physical mixture (approximately 80% within 60 min) before and after storage. The solid dispersion in SOL:EPO (1:1, w/w) was relatively stable at 40 ^{o}C/75% RH under CBZ tablet packaging conditions for at least 3 months. In conclusion, polymer combinations hat improve drug-polymer miscibility at an HME processing temperature below the Tm of a drug appear to be beneficial in the preparation of solid dispersions containing thermally unstable drugs [25].

CONCLUSION: Most of the natural or synthetic biomaterials currently on the market are based on polymers properties. Advances in synthetic organic chemistry and novel bioprocesses are enabling the development of a wide range of novel polymeric materials as candidates for developing drug delivery vehicles. The success of polymer blend lies in our ability to custom design or modify existing biomaterials to achieve appropriate biocompatibility, degradation and physical properties to elicit favorable biological responses.

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How to cite this article:
Muhaimin and Chaerunisaa AY: Polymer combination for parenteral drug delivery. Int J Pharm Sci Res 2017; 8(5): 1993-02.doi: 10.13040/IJPSR.0975-8232.8(5).1993-02