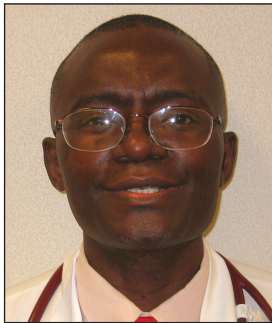


Carol Rees Parrish, R.D., M.S., Series Editor

# Elemental and Semi-Elemental Formulas: Are They Superior to Polymeric Formulas?



Diklar Makola

**Nutritional support, utilizing enteral nutrition formulas, is an integral part of the primary and/or adjunctive management of gastrointestinal and other disorders with nutritional consequences. Four major types of enteral nutrition formulas exist including: elemental and semi-elemental, standard or polymeric, disease-specific and immune-enhancing. Although they are much more expensive, elemental and semi-elemental formulas are purported to be superior to polymeric or standard formulas in certain patient populations. The aim of this article is to evaluate whether this claim is supported by the literature and to ultimately show that except for a very few indications, polymeric formulas are just as effective as elemental formulas in the majority of patients with gastrointestinal disorders.**

## INTRODUCTION

**T**he provision of nutritional support is an essential part of the primary and adjunctive management of many gastrointestinal (GI) disorders such as Crohn's disease, cystic fibrosis, pancreatitis, head and neck cancer, cerebrovascular accidents, etc. Nutritional support can be used to induce remission in Crohn's dis-

ease, facilitate "pancreatic rest" in pancreatitis and prevent nutritional depletion that accompanies many GI tract diseases. The factors leading to nutritional depletion include: 1) impaired absorption of nutrients; 2) inadequate intake due to anorexia; 3) dietary restrictions; 4) increased intestinal losses; and 5) an increase in nutritional demand that accompanies many catabolic states. Nutritional support can be provided by using either total parenteral nutrition (PN) or total enteral nutrition (EN), however EN when compared to PN has fewer serious complications (1,2) and is less expensive

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**Table 1**  
**Cost Comparison of Elemental and Standard Formulas**

<i>Product</i>	<i>Company</i>	<i>Cost \$/1000 kcal*+</i>	<i>Product</i>	<i>Company</i>	<i>Cost \$/1000 kcal*+</i>
<i>Elemental /Semi-elemental</i>			<i>Standard, Polymeric</i>		
AlitraQ (E)	Ross	29.17	Fibersource HN	Novartis	3.73
f.a.a. (E)	Nestle	28.00	Isocal	Novartis	7.60
Optimental (SE)	Ross	24.30	Isosource 1.5	Novartis	4.44
Peptamen (SE)	Nestle	24.06	Jevity 1.0	Ross	6.60
Peptamen 1.5 (SE)	Nestle	24.22	Jevity 1.5	Ross	6.60
Peptinex (SE)	Novartis	21.60	Novasource 2.0	Novartis	3.04
Peptinex DT (SE)	Novartis	18.58	Nutren 1.5	Nestle	3.72
Perative (SE)	Ross	8.68	Nutren 2.0	Nestle	2.99
Subdue (SE)	Novartis	19.79	Osmolite 1.0	Ross	6.94
Subdue Plus (SE)	Novartis	13.19	Osmolite 1.2	Ross	6.08
Tolerex (E)	Novartis	16.70	Probalance	Nestle	6.84
Vital HN (SE)	Ross	20.28	Promote	Ross	6.60
Vivonex T.E.N. (E)	Novartis	18.33	Replete	Nestle	7.35
Vivonex Plus (E)	Novartis	31.30	TwoCal HN	Ross	3.21

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\*Except for Nestle products, price does not include shipping and handling; +Per 800# on 11/7/05; E = elemental; SE = Semi-elemental; Note: Lipisorb, Criticare HN and Reabilan are no longer available; Used with permission from the University of Virginia Health System Nutrition Support Traineeship Syllabus (Parrish '05)

than PN. The EN formulas differ in their protein and fat content and can be classified as elemental (monomeric), semi-elemental (oligomeric), polymeric or specialized. Elemental formulas contain individual amino acids, glucose polymers, and are low fat with only about 2% to 3% of calories derived from long chain triglycerides (LCT) (3). Semi-elemental formulas contain peptides of vary-

ing chain length, simple sugars, glucose polymers or starch and fat, primarily as medium chain triglycerides (MCT) (3). Polymeric formulas contain intact proteins, complex carbohydrates and mainly LCTs (3). Specialized formulas contain biologically active substances or nutrients such as glutamine, arginine, nucleotides or  
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essential fatty acids (Table 1). Although elemental and semi-elemental formulas cost about 400% more than polymeric formulas (4) they are still widely used because they are believed to be 1) better absorbed, 2) less allergenic, 3) better tolerated in patients with malabsorptive states and 4) cause less exocrine pancreatic stimulation in patients with pancreatitis.

The aim of this paper is to evaluate whether there is evidence to support the superiority of elemental and/or semi-elemental formulas over polymeric formulas in providing nutritional support in patients with gastrointestinal diseases.

### **THEORETICAL BENEFITS OF ELEMENTAL AND SEMI-ELEMENTAL FORMULAS**

#### **Elemental (Monomeric) Formulas**

Elemental formulas contain individual amino acids, are low in fat, especially LCTs, and as such, are thought to require minimal digestive function and cause less stimulation of exocrine pancreatic secretion. In many products, MCT is the predominant fat source, and can be absorbed directly across the small intestinal mucosa into the portal vein in the absence of lipase or bile salts; they are believed to be beneficial in malabsorptive states. They are also considered to be advantageous in patients with acute pancreatitis (3), and in those with other malabsorptive states (5).

#### **Semi-elemental (Oligomeric) Formulas**

The nitrogen source of semi-elemental formulas are proteins that have been hydrolyzed into oligopeptides of varying lengths, dipeptides and tripeptides. The di- and tripeptides of semi-elemental formulas have specific uptake transport mechanisms and are thought to be absorbed more efficiently than individual amino acids or whole proteins, the nitrogen sources in elemental and polymeric formulas respectively (6). Silk, et al (7) found that individual and free amino acid residues, as found in elemental formulas, were poorly absorbed while amino acids provided as dipeptides and tripeptides were better absorbed. The semi-elemental formulas containing casein and lactalbumin hydrolysates, but not the fish protein hydrolysates, also stimulated jejunal absorption

of water and electrolytes. However, as will be discussed in subsequent sections, semi-elemental, as well as elemental, formulas have not been demonstrated to be superior to polymeric formulas (8–11).

Steinhardt, et al (10) found that although nitrogen absorption was better in total pancreatectomized patients who received hydrolyzed lactalbumin (semi-elemental formula) when compared to those who received intact lactalbumin (polymeric formula), nitrogen balance was similar between the two formula groups. The similarity in nitrogen balance between the two groups was most likely due to the significantly higher urea production in the hydrolyzed formula group. Of note, the patients in this study were not given pancreatic enzymes, the standard of practice in pancreatectomized patients.

### **COMPARISON OF ELEMENTAL AND/OR SEMI-ELEMENTAL TO POLYMERIC FORMULAS BY PATIENT/STUDY POPULATION**

#### **Malabsorptive States**

It is often assumed that most, if not all, patients with GI problems have varying levels of malabsorption and/or maldigestion and would therefore benefit from elemental or semi-elemental formulas. Malabsorption occurs as a result of a defect in the transportation of nutrients across the mucosa in conditions such as Crohn's, celiac disease or radiation enteritis, and only reaches clinical significance when 90% of organ function is impaired (12,13). On the other hand, maldigestion is due to intra-luminal defects of absorption such as pancreatic insufficiency, bile salt deficiency and bacterial overgrowth (14). Some of these digestive defects can be corrected by providing digestive enzymes or treating with antibiotics (12).

Patients considered to have malabsorption in the EN literature include patients who 1) have normal or moderately impaired gastrointestinal tract function, 2) are critically ill in the intensive care unit, 3) have undergone abdominal surgery or bowel resection or 4) have variations of the above who develop diarrhea after the start of EN. Most of these studies do not document the evidence and extent of malabsorption and/or maldigestion. In addition, many of these studies have not found

a significant difference in nutrient absorption and balance (8,15–17). Rees, et al (16) found that only a subgroup of 3 patients with extensive small bowel mucosal defects had “noticeably better nitrogen absorption and balance” when fed with a semi-elemental diet.

### Short Bowel Syndrome

Patients with short bowel syndrome (SBS) tend to be considered ideal candidates for elemental and semi-elemental formulas because of the malabsorption associated with SBS and the theoretical benefit of more efficient absorption. However, studies aimed at comparing the efficacy of elemental and semi-elemental formulas to polymeric formulas in patients with SBS have resulted in conflicting results. McIntyre, et al (9) found no difference in nitrogen or total calorie absorption between a semi-elemental and polymeric liquid formula in patients with <150 cm of jejunum ending in jejunostomy. In contrast, Cosnes, et al (11), found greater nitrogen absorption with consumption of a peptide based (semi-elemental) diet when compared to a whole protein (polymeric) diet in a similar group of patients. However, Cosnes, et al also found greater blood urea nitrogen and urea nitrogen excretion during feeding with the peptide-based diet than during whole protein feeding, suggesting that the additional absorption of amino acids resulted in an increase in amino acid oxidation. It is not known whether the increase in nitrogen absorption improved protein metabolism or nitrogen balance because these parameters were not measured (5).

In a more recent randomized crossover trial conducted in children with SBS, Ksiazek, et al (18) found no significant difference in intestinal permeability, energy, and nitrogen balance when diets with hydrolyzed protein were compared to those with non-hydrolyzed protein. There is insufficient evidence to suggest that the more expensive elemental or semi-elemental formulas are superior to polymeric formulas in patients with SBS (19).

### Hypoalbuminemia

Elemental and semi-elemental diets are purported to be beneficial in improving tolerance to EN and reduce the development of diarrhea when given to patients with

hypoalbuminemia. This assumption was based on case series reports by Brinson that seemed to suggest that these formulas resulted in increased nitrogen absorption and reduced stool output when given to hypoalbuminemic patients (20,21). However, a randomized clinical trial aimed at comparing a peptide based enteral formula with a standard formula concluded that the peptide formula offered no advantage to the standard formula (22). Studies by Viall and Heimburger (23,24) also found that semi-elemental compared to standard polymeric EN was equally well tolerated and resulted in similar digestive or mechanical complications—such as diarrhea, vomiting and high gastric residuals. The nitrogen balance was similar with both formulas in the Viall (23) study while Heimburger, et al (24) found that the peptide formula resulted in a slightly greater increase in serum rapid-synthesis proteins such as the surrogate markers, prealbumin and fibronectin, especially between days 5 and 10. However, prealbumin levels are also affected by other disease-related factors such as infection, cytokine response, renal and liver failure and do not necessarily reflect nutritional status (19) thus making the significance of this finding unclear.

### Crohn's Disease

Enteral nutrition is effective in inducing remission in patients with uncomplicated, active Crohn's disease (25–28). Meta-analyses of EN versus corticosteroids have found that although corticosteroids are superior to EN in inducing remission (29–31), EN is also efficacious with expected remission rates of up to 60% on an intention to treat basis (25,29,30).

#### *The Effect of Enteral Nutrition Protein on Crohn's Disease Remission*

Elemental formulas are thought to induce remission in Crohn's disease patients by providing chemically synthesized amino acids that are entirely antigen free thus limiting the patient's exposure to dietary antigens that may precipitate or exacerbate a Crohn's flare. Giaffer, et al (32) found a significantly higher clinical remission rate (based on reduction in Chronic Disease Activity Index (CDAI) scores) after 10 days of an elemental formula (Vivonex), compared to a polymeric formula (Fortison), 75% versus 36% respectively.

However these findings have not been replicated in other studies (33–35). Rigaud, et al found no significant difference in clinical remission rates based on CDAI scores measured during the last 7 days of a 28 day period between Crohn's disease patients treated with elemental (Vivonex HN) versus polymeric EN (Reamentyl or Nutrison) (35). The remission rates were 66% in the elemental group and 73% in the polymeric group. The CDAI seemed to improve more rapidly in the elemental group with a remission rate of 60% achieved by day 14; however, the difference in remission rates at day 14 was not statistically significant. Verma, et al also found that although clinical remission seemed to occur earlier in the elemental group, time to remission was not statistically different (34). Ludvigsson, et al found that 16 children with Crohn's disease who received an elemental (Elemental 028 Extra) versus 17 who received a polymeric (Nutrison Standard), had similar remission rates (69% versus 82%) (33). Patients treated with the polymeric formula gained more weight even after controlling for maximum caloric intake per kilogram of body weight.

Two meta-analyses based on clinical trials that compared elemental to non-elemental or polymeric formulas found no significant difference in clinical remission rates among patients managed with the different formulas (29,31). These results suggest that elemental formulas are not superior to non-elemental or polymeric formulas in inducing remission and that avoiding dietary protein in the formula is unlikely to be the mechanism by which EN induces Crohn's remission.

### ***The Effect of Enteral Nutrition Fat on Crohn's Disease Remission***

Some researchers have hypothesized that the beneficial effect of EN on Crohn's remission may be due to the fat content of the formula. It has been suggested that n-6 polyunsaturated fatty acids (PUFAs) such as linoleic acid, a precursor of arachidonic acid, leads to increased production of inflammatory eicosanoids such as prostaglandin E<sub>2</sub>, thromboxane A<sub>2</sub> and leukotriene B<sub>4</sub>, which may be detrimental in Crohn's disease (36); while n-3 PUFAs such as  $\alpha$ -linolenic acid, precursors of eicosapentaenoic acid and docosahexanoic acid which lead to the production of the less inflammatory series-3 prostaglandins and leukotiene B<sub>5</sub> (36), may be

protective. Increased amounts of n-3 PUFAs also inhibit arachidonic acid production thus reducing the production of the pro-inflammatory eicosanoids (36).

To test the hypothesis that altering fat content may prove beneficial in Crohn's, Bamba, et al (37) randomly allocated 28 patients to low fat, medium fat and high fat elemental diets containing 3.06, 16.56, and 30.06 g/day of fat. The 3 formulas had identical total calories, nitrogen source, vitamins and minerals but differed in their fat and carbohydrate content. The remission rates after 4 weeks of treatment were 80%, 40% and 25% respectively, thus favoring the low-fat group. The extra fat in the medium and high fat groups was made up of long chain triglycerides and contained 52% linoleic, 24% oleic and 8% linolenic acid. Bamba, et al (37) concluded that the high fat content in elemental formulas consisting mainly of n-6 PUFAs or long chain triglycerides (LCT) decreased the therapeutic effect of enteral formulas.

Leiper, et al (38) compared a low LCT to a high LCT polymeric EN. The low LCT provided 5% of energy as LCT with MCT providing 30%. The high LCT provided 30% of energy with MCT providing 5% energy. The linoleic acid content was similar between the two formulas (7.4% versus 9.5%), but the high LCT contained 36% of oleic acid compared to 3.4% in the low LCT group. The formulas were identical in color, carbohydrate, total fat, minerals, trace elements and vitamin levels. Overall remission rates were unexpectedly low in both groups with no significant difference between the two formulas, (low LCT 33% versus high LCT 52%) thus making it difficult to compare the efficacy of the two formulas in this study (36). The poor responses were unlikely to be due to the effect of linoleic acid content in the enteral formula since both formulas had low concentrations of linoleic acid.

Gassull, et al (39) compared polymeric formulas containing either high oleate (79% oleate, 6.5% linoleate) or low oleate (28% oleate, 45% linoleate) content. The total LCT and MCT were similar in the two groups. A third group was randomly allocated to oral prednisone (1 mg/kg daily). Contrary to expectations, the high oleate/low linoleate group, which was expected to have higher remission rates, had significantly lower remission rates when compared to both the low oleate/higher linoleate and steroid groups

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(20% versus 52% and 79%). The authors concluded that excess synthetic oleate may be responsible for the low remission rates seen in the high oleate/low linoleate group (39).

Sakurai, et al (40) found no significant difference in remission rates in Crohn's patients when a low fat elemental formula (3.4 g per 2000 kcal dose) was compared to a protein hydrosylate, high fat formula (55.6 g fat per 2000 kcal dose) (67% in the low fat elemental formula group and 72% in the high fat semi-elemental formula group). Most of the fat in the high fat group came from MCT. They concluded that it is not necessary to restrict the MCT content of enteral formulas (40). Based on Bamba, et al's (37) study in which the high fat group did poorly, and based on the theoretical disadvantage of LCT, especially linoleic acid, Gorard, et al (36) argue that high LCT and /or linoleic acid in enteral formulas may attenuate the effect of EN in inducing Crohn's disease remission. Based on Gasull, et al's study excess synthetic oleate may also be detrimental (39).

### Cystic Fibrosis

Maintaining good nutritional status, though often difficult to achieve, is positively correlated with a good prognosis and survival in patients with cystic fibrosis (CF). Several studies have shown that long-term nocturnal EN supplementation in patients with cystic fibrosis helps maintain nutrition and slows down the decline in pulmonary function. It is now recommended that CF patients whose weight for height is less than 85% of ideal, and who fail to respond to a 3-month trial of non-invasive nutritional interventions, should receive EN (41). However, CF centers differ in their recommendations on the type of enteral formula and the use of pancreatic enzymes in patients requiring EN.

In a cross-over trial comparing Peptamen (semi-elemental formula) and Isocal (polymeric formula) with pancreatic enzymes added in 4 to 20 year-old patients with cystic fibrosis and pancreatic insufficiency, Erksine, et al (4) found no significant difference in fat and nitrogen absorption or in weight gain between the two groups. Pelekanos, et al (42) also found no significant difference in rates of protein synthesis and catabolism among patients managed with Criticare HN (semi-elemental), Traumacal (polymeric)

and Modified Traumacal (modified polymeric with less protein and fat when compared to Traumacal) formulas. Because there are no studies that demonstrate the superiority of elemental or semi-elemental over polymeric formulas, using the less expensive polymeric formula supplemented with pancreatic enzyme supplements would be more cost-effective (43).

### Acute Pancreatitis

Historically, PN has been the standard method of nutritional support in patients with severe acute pancreatitis. The use of PN was aimed at avoiding exocrine pancreatic stimulation and providing "pancreatic rest" while providing nutrition to the patient (1). However, recent data suggests that EN delivered distal to the Ligament of Treitz is well tolerated, results in fewer infectious complications, and is less expensive than PN (1,2,44-47). Most EN studies in this patient population have utilized the more expensive elemental formulas, in the belief that they do not require pancreatic stimulation for absorption and are therefore least likely to stimulate the pancreas (43,48). However, jejunal polymeric EN is also well tolerated by patients with acute pancreatitis and can potentially be used to facilitate pancreatic rest (46,47,49,50). Furthermore, because of concerns that the increased fat content or intact proteins in polymeric formulas will cause increased pancreatic stimulation and slow the resolution of pancreatitis (2,51), clinicians still prefer to use elemental or semi-elemental jejunal formulas in patients with acute pancreatitis. However, polymeric formulas have also been successfully used in long-term enteral nutrition in patients with chronic pancreatitis (43,52). No studies have compared elemental or semi-elemental formulas to polymeric formulas in patients with acute pancreatitis.

### Radiation Related GI Tract Damage

Elemental and semi-elemental formulas have also been tried in patients with gastrointestinal problems related to pelvic and abdominal radiotherapy. In a review of studies involving 2,646 patients who underwent radiotherapy for gynecologic, urologic and rectal cancer in the UK, the authors noted that 50% of patients developed chronic bowel symptoms and 11%-33% developed

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malnutrition requiring some form of nutritional management (53). These studies all varied in design and validity, none of which could be combined into a meta-analysis since the interventions and outcomes were different. The nutritional interventions were implemented either during or after completion of radiation therapy and included low fat diets, low residue diets, elemental diets versus modified or polymeric diets or parenteral nutrition, lactose free and gluten free diets, as well as use of probiotics and micronutrient supplements. Three of the studies included in the above review found that elemental diets reduced the incidence and severity of diarrhea symptoms. However the largest of these 3 papers—674 patients—was only published as an abstract in a non-peer reviewed summary booklet. The authors concluded that there was no evidence to suggest that nutritional interventions could prevent or manage bowel symptoms attributable to radiotherapy, but that low-fat diets, probiotic supplementation and elemental diets merited further investigation.

### HIV Related Disease

Nutritional trials conducted in HIV positive patients have tested either 1) specialized, immune-enhancing supplements/formulas in which a polymeric formula is fortified with omega 3 fatty acids and or arginine versus non-fortified formulas (54,55); 2) elemental versus polymeric formulas (56–58) and 3) nutritional counseling plus usual diet versus nutritional counseling plus usual diet and nutritional supplementation (59,60).

Pichard, et al found that arginine and omega 3 fatty acid enriched formulas did not improve immunological parameters when compared to a non-enriched formula with similar amounts of calories and protein. Both groups experienced a similar significant weight gain. In contrast to these findings, Suttman, et al (54) in a crossover double-blind trial in which a polymeric formula fortified with n-3 polyunsaturated fatty acid and arginine was compared to a polymeric non-fortified formula, found that the enriched formula resulted in significant weight gain and an increase in soluble tumor necrosis factor receptor proteins, thus theoretically modulating the negative effects of tumor necrosis factor.

In the studies by Rabeneck, et al and Schwenk, et al nutritional counseling, rather than nutritional supple-

mentation, resulted in an overall improvement in nutritional intake and nutritional outcomes (59,60). Gibert, et al found no significant difference in percent weight change and body cell mass after 4 months of supplementation with a peptide based formula when compared to a whole protein based formula (57). Similarly, Hoh, et al (58) found no significant difference in gastrointestinal symptoms, body weight and free fat mass between HIV patients supplemented for 6 weeks with a whole protein-based compared to those supplemented with a peptide-based formula (58). De Luis Roman (56) found that 3 month supplementation with a peptide based, n-3 fatty acid enriched formula resulted in a significant increase in CD4 counts when compared to supplementation with a non-enriched, standard and whole protein based formula. Both formulas resulted in a significant and sustained increase in fat mass weight while there was no change in fat free mass and total body water (56).

Finally, Micke, et al compared two different types of whey protein based formulas and found that after two weeks of supplementation both supplements resulted in a significant increase in glutathione levels (61). These studies suggest that elemental and semi-elemental formulas are not superior to polymeric formulas in improving the nutritional status of patients with HIV, but that there may be some evidence of an immunologic benefit, with or without a nutritional benefit, when specialized formulas enriched with n-3 fatty acids are compared to non-enriched formulas.

### Chyle Leak

Most of the nutritional recommendations in managing patients with chyle leak are based on case series and theoretical considerations. A more extensive review of this subject appears in the May 2004 edition of *Practical Gastroenterology* (62). The objective of nutritional management is to reduce chyle fluid production by eliminating LCT from the diet, replace fluid and electrolytes while providing adequate nutrition to maintain nutritional status, correct deficiencies or prevent malnutrition. For those patients who are able to tolerate food by mouth, a fat-free diet given with MCT, fat-soluble vitamins and essential fatty acid (EFA) supplements should be attempted. However, for those patients who require EN, a very low fat elemental, MCT-based

formula should be used. These formulas typically provide an adequate amount of EFA and fat-soluble vitamins. Alternatively, (for short-term trial only), a more economical option would be to use a fat-free liquid nutritional supplement combined with a multivitamin/mineral supplement, a fat free protein supplement and small amount of safflower oil to provide EFA.

## CONCLUSION

There is no evidence to suggest that elemental and/or semi-elemental formulas are superior to polymeric formulas when used to provide nutritional support and treatment in patients with most gastrointestinal diseases that are likely to cause maldigestion and malabsorption. In patients with maldigestion, it may indeed be less expensive to treat the underlying problem such as pancreatic insufficiency, celiac disease or small bowel bacterial overgrowth, with digestive enzymes, a gluten free diet/formula or an antibiotic respectively, rather than use an expensive elemental formula. The mechanism by which enteral feedings achieve remission in Crohn's disease is still not well understood and needs further research. Specialized or immune-enhancing formulas (fortified with n-3 fatty acids) may be beneficial in enhancing immunity, but not necessarily the nutritional status, of patients with HIV when compared to non-fortified formulas. Although randomized trials of elemental and polymeric EN in the management of patients with pancreatitis are lacking, EN using a polymeric formula administered beyond the Ligament of Trietz may be as effective, as well as safer, than PN. Elemental and semi-elemental formulas, for the most part, should be reserved for those patients who have failed a fair trial of several polymeric formulas before considering the parenteral route. ■

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