INTERNATIONAL RESEARCH JOURNAL OF PHARMACY ISSN 2230 – 8407
Available online http://www.irjponline.com
Review Article

FORMULATION DEVELOPMENT OF ENTERAL NUTRITION PRODUCTS

Mirajkar Reshma Nilesh*[1], Patil Amol Vilas[1], Jamadar Shahaji Ambadas[1], Mirajkar Nilesh Sharadchandra[2]
[1]AISSMS College of Pharmacy, Kennedy Road, Pune- 411001, India
[2]Senior Product Manager, Zyphar's Pharmaceutics, Pune-411004 India

Article Received on: 14/01/2011 Revised on: 20/02/2011 Approved for publication: 11/03/2011

*Mirajkar Reshma Nilesh, (Master in Pharmacy), Assistance Professor, AISSMS College of pharmacy, Department of Pharmaceutics, Kennedy road, Pune-411001, Maharashtra, India Email: reshmamirajkar@gmail.com

ABSTRACT
This review mainly deals with the Formulation Development of Enteral Nutrition Products. Nutrition plays an important role in the prevention and management of many diseases. Chronic illness is associated with many complications such as anorexia, hypermetabolism, malabsorption, atrophy of muscles, liver, kidney, gastrointestinal tract heart, and impaired cell mediated immunity, susceptibility to infection, poor wound healing, anaemia, death. Hence it is important to correct caloric and nutrient deficiencies whenever possible. The term enteral means "within or by the way of gastrointestinal tract". The nutrition product given by enteral route called as enteral nutrition product. The different types of enteral nutrition are classified as Short term and long term enteral nutrition. Enteral tubes are made of PVC, Polyurethane etc. The selection of the enteral formula is patient specific thus its nutritional requirements, the ingredients used in it are taken into consideration. The classification of formulas is also done on the basis of the patient's needs and ingredients used in it. The enteral feeds can be given in the form of solutions and powders which require reconstitution. The quality control test like Osmolality, pH, etc is also taken into consideration. Thus, the purpose here is to point out explicitly the formulation development of enteral nutrition products.
KEYWORDS: Enteral Nutrition, Ryle's Tube, Nutrient Composition, Micronutrients, Additives

INTRODUCTION

Nutrition

Nutrition may be defined as utilisation of food by living organisms. It significantly promotes man's development health and welfare[1]

Importance of Nutrients

Nutrition plays an important role in the prevention and management of many diseases. None today would challenge the concept that nutritional support is an integral and essential element in the care of the patient who is critically ill nutritionally, depleted or both. Patients unable to consume necessary nutrients orally require alternative form of nutritional support. Chronic illness is associated with many complications such as anorexia, hypermetabolism, malabsorption, atrophy of muscles, liver, kidney, gastrointestinal tract heart, and impaired cell mediated immunity, susceptibility to infection, poor wound healing, anaemia, death. Hence it is important to correct caloric and nutrient deficiencies whenever possible. Patients need adequate nutrition to recover from any illness. Patients who are critically ill have high nutritional requirements and can become malnourished very quickly.

Enteral Route And Enteral Nutrition

The term enteral route means "within or by the way of the gastrointestinal (GI) tract."

The nutrition product given by enteral route is called as enteral nutrition product.

Commercially available liquid nutritional supplements are generally referred to as oral supplements and "enteral feeding" and "tube feeding" are used interchangeably[2]

ENTERAL NUTRITION

The best way to feed a patient is using their own gastrointestinal tract (stomach and bowel). Feeding by the gastrointestinal tract is called "Enteral Feeding". We also refer to this as feeding through the gut. Because patients cannot swallow food if they have a breathing tube in their throat, they are fed through a feeding tube. An especially sterile designed solution that contains the nutrients is specifically made for patients who have difficulty in swallowing, thus patients recovery is possible.

Need Of Enteral Feeding

1] Enteral nutrition is for patients who are unconscious and sedated.

2] It is for patients who have an eating or swallowing problem and thus making it impractical for intake of nutritional requirements orally.

3] Enteral feeding is to be done where nutritional requirements cannot be taken orally; the placement of tubes in GI tract is simple and low risk. Due to this, the use of this feeding is in demand.

Types of Enteral Feeds

Enteral feeds can be given by any of the 3 ways. They are Bolus, Intermittently and Continuously. Bolus is very simple requiring minimal equipment but increases the risk of GIT. It can be given by gravity. Intermittently gives time freed of feeding but increases risk of GIT. It is by gravity or pump. Continuously has an advantage of reducing GI symptoms. It is pump system. Fig 1

CLASSIFICATION OF ENTERAL NUTRITION

Types of enteral nutrition are classified depending on the duration of time and the route of administration. Fig 2

Short Term Enteral Nutrition

The duration of time for short term enteral nutrition is less than 30 days .The preferred route of administration is nasal route. If a tube is inserted through a nose, it is nasal route. They are further classified as:

A] Nasogastric Route

Tubes that end in the stomach are called "gastric" tubes or G tubes. The gastric part is the preferred site and so this is called as Nasogastric route. Small-calibre NGTs are used solely for feeding, whereas larger ones can be used to decompress the stomach, monitor gastric pH, and provide medications or feedings. A fine bore tube. eg: vygon Fr .8 nasogastric tube (a PVC tube without guide wire) is recommended when enteral nutrition is required for less than 2 weeks, or if a new tube needs to be passed every night . Where the duration of feeding is over 2 weeks, a fine bore tube Eg: Flocare Fr 8 (a polyurethane tube with a guide wire) is used. The nasogastric tube should be replaced every 6 weeks if gastrostomy is not indicated.

E.g.Flocare Fr. 8 is wide enough for all types of feed and is comfortable for most patients.

Advantages:

1] Small bore tubes should be used than larger ones because of comfort.

2] These tubes are suitable for short-term use

Disadvantages: 1] Nasally placed tubes can cause local irritation, epistaxis, and sinusitis.

2] The larger bore tubes can result in patient discomfort and frequent self-extubation.

B] Naso- Jejunal Route

The site of administration is jejuna. A tube inserted into the jejunum is called as "J" tube or jejuna tube. Flocare or Corflo Merck feeding tubes are used for Naso jejuna tubes. They are usually inserted by a radiologist or endoscopist.

Eg: Patients who have gastro paresis may benefit from Naso – jejuna feeding.

Advantages:

1] Generally smaller in size compared with NGT's

2] They cause less discomfort

Disadvantages: Clogging of the tubes with nutrients or medications is more prevalent

C] Naso-Duodenal

The stomach empties toward the right side and into the small bowel. The initial segment of the small bowel (or small intestine) is called the duodenum. A tube that ends in the duodenum is called a duodenal tube. Nasal route is the preferred route of administration and duodenal is the preferred site of administration. Thus it called as Naso-duodenal.

Advantages:

1] Generally smaller in size compared with NGT's

2] They cause less discomfort

Disadvantages: clogging of the tubes with nutrients or medications is more prevalent

Long Term Enteral Nutrition

The duration of time for long term enteral nutrition is more than 30 days. Patients with agitation and self extubation are best managed by long term nutrition. They are further classified as

1] Gastrostomy

If a tube inserted through a puncture site can be identified by the end of the word. A puncture hole is called a "stoma" or "ostomy". A stomach tube that is inserted through a puncture is called as gastrostomy. Gastrostomy tube insertion should normally be considered if it is anticipated that the enteral feeding will be required beyond 4 weeks. It should also be considered where it is difficult to pass a nasogastric tube due to obstruction, and where nasogastric tubes are having a re-passed frequently.

Gastrostomy is further classified on the basis of mode of action as follows:

A] PEG B] RIG C] PIGG

A] PEG

A puncture through the skin is called "percutaneous". A feeding tube inserted through a puncture wound is called a Percutaneous feeding tube. It is inserted endoscopically and held in place with an intentional retention dome. A change of tube is recommended after every 1 year .They can be removed by traction.

B] RIG

RIG is "Radiological inserted gastrostomy tube". It is inserted radiologically and is held in place with an intentional retention balloon. It can last for 4 – 6 months. The balloon tube gastrostomy tube is used as replacement. It is indicated for patients who have

obstructing lesions in upper GI tract, which prohibits the passage of an endoscope, or where tumour seeking is a risk. If an obstruction to passing the endoscope is anticipated, or if a PEG insertion fails, then RIG is the preferred method of insertion.

C] PIGG

PIGG is "Pre-oral imaging-guided gastrostomy tube". It is inserted radiological and is held in place with an intentional retention dome. A change of tube is recommended after every 1 year. They can be removed by traction

Advantages

1] It is cosmetically pleasing.
2] It decreases skin irritation.
3] It lowers risk of migration and dislodgement.

Disadvantages

1] Mature gastrostomy site is required.
2] The valve leaks and is of limited sizes.
3] It is more expensive than conventional tubes.

2] Jejunostomy

A jejunal tube inserted through a puncture is a jejunostomy. An open surgical jejunostomy should be anticipated during the primary surgical procedure. In exceptional circumstances, this is required as a primary procedure. This tube can be inserted during surgery, or by a radiologist or endoscopist. Eg: In patients with history of gastro – oesophageal reflux.

Advantages:

1] Pump-controlled infusions are recommended for jejunal feedings given by Continuous infusion to decrease gastroesophageal reflux

2] Jejunal access is appropriate in patients with a history of tube feeding. Pneumonia or reflux esophagitis.[3, 4]

The type of nutrition is mainly based on the route of administration and the tube used in this route is of utmost importance. So the tube composition is as follows

Tube Composition

Enteral tubes are made of various materials such as polyvinyl chloride, silicone (silastic) or latex and polyurethane.

Tubes

1] Polyvinyl chloride:

Polyvinyl chloride is easy to place and it resists collapse but there is a risk of perforation and should be replaced every 3 days.

2] Silicone:

Silicone or silastic is pliable. It has a small diameter and is more comfortable than polyurethane.

3] Polyurethane:

It is more comfortable for long term feeding but is not as comfortable as silicone tube.[5]

Ryle's Tube Fig 3

These are manufactured from non toxic, non irritant PVC. These are specially designed for nasogastric introduction for nutrition and aspiration of intestinal secretion. Distal end is coned with corrosion resistant stainless steel balls sealed into the tube to assist the passage of tubing during intubation. Radio opaque line provided throughout the tube for X-ray visualization. Proximal end is provided with universal funnel connector for easy extension. These are sterile individually packed in peelable pouch pack.[6]

Levin's Tube Fig 4

These are designed for nasal and gastric introduction for nutrition and aspiration of intestinal secretion. These are siliconized & smooth outer surface to reduce chances of tissue irritation. These are made up of thermosensitive material, softening to body temperature conforming to the shape of Nasogastric tract. These are provided with full length radio-opaque line for checking the tube placement. The provision is given for three eye-holes for efficient aspiration. Soft tapered connector at the proximal end to fit easily with standard accessories. These are sterile, non - toxic and pathogen free.[7]

FORMULATION OF ENTERAL NUTRITON PRODUCTS

Taking into the consideration goals and feeding of enteral nutrition, the study of formulation aspect is of utmost importance. The selection of an enteral formula must be patient specific. The functioning and capacity of the GI tract, underlying disease states and patient tolerance must be assessed to determine which formula should be selected. Many formulas are very similar in composition, varying only slightly in nutrient content. It is important to be familiar with the properties of commonly used enteral formulas.

Goals of Feeding

1] Selection of an appropriate formula
2] Formula delivery
3] Indications of nutritional status[3]

Formulation needs to have nutritional requirement and they are as follows:

Nutritional Requirement

1] The recommended dietary allowances serve as initial guidelines in the selection and modification of a formula.
a) All nutrients of the final formula should be calculated and compared with RDA for age or for the development of delayed child for height.
b) Vitamin mineral supplementation may be needed.

2] The disease process itself indicates whether the requirements are changed

3] Drug induced nutritional deficiencies may develop from long-term use of medication that affects

a) Nutrient function and metabolism.
b) Decrease nutrient absorption or synthesis.

Nutrient Composition

The formulation of enteral nutrition products involves active ingredients, additives, and vehicle. Fig 5

A] Active Ingredient

The active ingredient can be given alone or in combinations as per conditions and the treatment required to it. The active ingredients are

1] Carbohydrate

Carbohydrate acts as an energy source .Carbohydrate sources must be soluble, digestible and have a low osmolality. Commonly used carbohydrate sources include corn syrup solids, hydrolyzed cornstarch, maltodextrins and other glucose polymers. Some speciality formulas include various types of fiber, fructose. Simple sugars (sucrose and glucose) enhance the palatability of oral supplements but increase osmolality. The percentage of total calories from carbohydrate varies from 30% to 90% depending on the condition for which the product was formulated. The majority of enteral nutrition products do not contain lactose, so should not be a concern in lactose-intolerant patients.

2] Lipids

Lipids provide an isotonic, caloric dense energy source. Corn and soybean oil are commonly used lipid sources in enteral formulas. Canola and safflower oils may also be found. These vegetable oils contain mostly long-chain triglycerides. They contribute essential fatty acids, limit osmolality, and enhance palatability. Vegetable oil contains variable amount of essential fatty acids. As it is isotonic, it reduces the potential for hyperosmotic diarrhoea.

Fat content of enteral formulas varies from 1% to 55% of total calories according to the formula's intended use. Medium-chain triglycerides (MCT) do not require bile salts or pancreatic lipase for absorption and may be used in patients with lipid malabsorption disorders. However, MCT oil does not contain essential fatty acids and may cause delayed gastric emptying, leading to poor tolerance. Fat enhances palatability and flavour of formula. Suggested EFA intake especially linoleic acid is 3% to 4% total calorie needs.

For example, products designed for pulmonary disease and glucose intolerance are high in fat, whereas products designed for intestinal malabsorption contain decreased amounts of total fat.

3] Protein

Protein may be delivered as intact protein, partially digested protein, or free amino acids. Choice of product is based on the patient's disease state and the ability to absorb the protein. Commonly used protein sources include caseinates and soy protein isolates. Polymeric formulas contain these intact proteins. Oligomeric formulas contain enzymatically hydrolyzed casein or whey. Monomeric or elemental formulas contain free amino acids. The protein content of formulas ranges from approximately 4% to 32% of total calories. Products designed for renal disease may contain virtually no protein, whereas stress and immune-enhancing formulas contain up to 80g/1000kcal. Specialized enteral formulas may be enhanced with branch-chain amino acids, glutamine, or arginine.

B] Additives

Various additives used are as follows

1] Micronutrients

It constitutes of vitamins and minerals which are provided in adequate volume to meet 100% of the RDA. However, the volume required to provide the RDA varies greatly among products from one to four litres.

2] Fiber

Fiber is added to enteral formulas to improve stool consistency. The most commonly added fiber is soy polysaccharide; an insoluble fiber. This soy fibre helps to maintain normal bowel movement. Other insoluble fibers are cellulose, hemicelluloses, and lignans. Soluble fibers are guar gum, oat fiber, and pectin. Fiber-containing formulas can create complications in patients who are fluid restricted or have delayed GI transit. Content of fiber supplemented formula ranges from 5 to 14 g of fiber per litter. Recommended intake of dietary fiber is approximately 20 to25 g / day .Fiber intake of less than 30 g / day did not seem to impair vitamin, mineral or drug bioavailability in the gut. The major role of fibre in enteral formulas is likely the contribution of short chain fatty acids, which are trophic for bowel mucosa. Because fibre has a potential protective effect for multiple disease sates , including diverticulosis , colon cancer, diabetes and heart disease , it may have a role for patients in long term care facilities or patients who will require enteral formulation for a prolong period of time.

C] Vehicle

The vehicle used is water.

Water

Enteral preparations are aqueous based preparations. Water is the vehicle used and in case of powders they are used for reconstitution purpose. Most of enteral formulas contain water in the general range of 690 to 860 ml per 1000ml of enteral formula. Standard infant formulas are 0.67 calories/cc. whereas adult formulas are 1 calorie/cc or 1.5 to 2.0 calories/cc. Quantity water in the enteral formulas is often described as water content or moisture

content. Caloric density of a formula is dictated by the amount of water contained in the formula. Formulas that provide 1 kcal/ml are approximately 85% water. Formulas that provide 2kcal/ml are approximately 70% water.[3]The following table shows different caloric density according to water content of the formula. Table1 Depending on the composition of the enteral nutrition and the patients need, the classification of formulas is done. It is as follows

Classification Of Formulas

1] Polymeric Formulas

Most of patients who are critically ill may be enterally fed with polymeric formula. Nitrogen balance has been reported to be similar for patient with normal digestive and absorptive capacity who was fed intact protein, partially hydrolyzed protein, and amino acids with approximately the same amino acid profiles.

Lactose-Containing/Lactose-Free Diets (Polymeric Diets)

Formulations containing lactose are rarely used today. Many patients referred for enteral feedings have genetic or acquired lactase deficiency. Lactose-free mixtures are the basic feeding formulations and are designed for long-term usage. They generally provide 1 kcal/mL and are isotonic, although they may be concentrated to 1.5-2.0 kcal/mL A standard formulation has 12%-20% of its calories from protein, 45%-60% of its calories from carbohydrates, and 30%-40% of its calories from fats. They contain complex forms of carbohydrates, fats, and proteins and require some degree of digestion and absorption. The use of the product containing lactose would result in abdominal distention, cramping and diarrhoea.

2] Partially Hydrolyzed Formulas

These are macronutrients which may be partially or completely hydrolysed via enzymatic activity into smaller components. It is indicated for patients with partial digestive and absorptive capacity. Patients with resolved acute illness might be capable of transition from partially hydrolyzed formulas to polymeric formulas. Composition may vary in free amino acids and peptides, type and quantity of fat, content of carbohydrate content. Some formulas may have unpleasant taste and odour. Most of the formulas are expensive.

3] Disease-Specific Formulas

Some formulas are designed for specific organ dysfunction and some are for metabolic stress.

Pulmonary Formulas

Most standard formulas provide most nonprotein calories as carbohydrates. Carbohydrates are metabolized with a higher respiratory quotient than lipids. New formulations are available that provide a majority of calories as fat (55%) and maintain the respiratory quotient below 1.0 so that less CO_2 is produced per unit of oxygen consumed. This may be beneficial in the intubated patient with lung disease who may be difficult to either oxygenate appropriately or wean from the ventilator. For most patients with pulmonary disease, meeting caloric needs with a standard polymeric formulation is recommended. The most important issue is to provide adequate nutritional support and avoid overfeeding, which produces a substantially greater increase in CO_2 production because the respiratory quotient for converting carbohydrates to fat exceeds 1.0. In patients with CO_2 retention and pulmonary failure, the ratio of carbohydrate to fat calories within an enteral formulation may have some impact.

Renal Failure Formulas

Patients with renal failure may benefit from a formula that minimizes blood urea nitrogen formation, slows the rate of renal failure progression, and meets nutritional needs. This would be especially important for those patients with marginal renal function who are attempting to avoid dialysis therapy or patients who are not dialyzed on a regular basis. Enteral nutrition products designed for patients with renal failure are low in protein, phosphorus, magnesium, potassium, and sodium. Special formulations are available that contain primarily the essential amino acids. The premise is to use urea for the production of required nonessential amino acids, ultimately reducing urea waste. Certain types of enteral products may be appropriate based on the level of renal impairment. In patients with glomerular filtration rates below 25 mL/min but not on dialysis, low-protein diets providing 0.28 g protein / kg /day

With essential amino acid supplementation may be beneficial

4] Modular Diets

Modular feedings consist of individual nutrient components that are mixed to create a specific enteral formulation or can be added to an existing one. They exist as separate nutrient units: fat, carbohydrate, or protein. Thus, a custom enteral solution can be devised or individual components added to a commercial formula to obtain higher levels of a particular nutrient. One purpose for using modular formulas is supplemental use it may add calorie or protein density. Tailor tube feeding to individual nutritional needs as a supplement to commercial enteral formulas.

Advantage: It can be de novo formulated for individualized designed of nutrient formula to meet specific nutrient needs of an individual.

Advantages of de novo enteral formulation include

1] Customizing the formula to meet specific nutrient composition of the patient

2] Select cases using de novo formulas have reported cost savings.

Disadvantages of de novo formula include

1] Complexity of ordering specific nutrient composition as well as the method and rate of tube feeding administration unless a standardized orders form is used.

2] Increased cost of labour

3] Complexity of calculating nutrient composition

4] Potential risk of bacterial contamination from excessive handling of formulas

5] Potential physical incompatibilities with insoluble components.

5] Elemental Diets (Monomeric and Oligomeric Diets)

Elemental or chemically defined formulations are designed for use in patients with "limited" digestive capacity. This may include diseases in which the bowel's absorptive capacity is functionally or surgically reduced, such as Crohn's disease or short bowel syndrome. They are delivered as free amino acids alone (Monomeric) or free amino acids, dipeptides, and tripeptides (Oligomeric) that can be absorbed via active transport mechanisms without preliminary intraluminal hydrolysis. They may be combined with easily absorbed fats (medium-chain triglyceride oil) and/or carbohydrates (maltodextrins). Elemental diets are fiber-free, and because of the presence of multiple small particles, they are highly osmotic. There is no advantage in using an elemental diet in a patient with a normal gastrointestinal tract. Elemental diets are much more expensive than polymeric formulas, and the poor taste usually precludes adequate oral ingestion and necessitates tube feeding. Newer flavour packets are available and may improve the taste and patient acceptance.

6] Specialty Diet Products

Specialty formulations are available for the patient with unique nutritional requirements. Glutamine is a nonessential, neutral amino acid derived from skeletal muscle breakdown. It is essential for rapidly dividing cells and it is actively metabolized by the small intestine, where it serves as both a nitrogen donor for nucleic acid synthesis and an energy source. It has been shown to maintain small bowel mucosa when placed in parenteral solutions as compared with glutamine-free parenteral formulations. Arginine is a nonessential amino acid that, in supra, physiological amounts, has been shown to increase nitrogen retention, accelerate wound healing, and enhance immune functions. Postsurgical cancer patients who were tube-fed an enteral diet containing arginine, structured lipids, RNA, and menhaden oil improved invitro immune responses and nitrogen balance compared with controls who were fed a standard enteral diet.

7] Blenderized Diets

Blenderized formulations are a combination of table foods with added vitamins and minerals. They contain a generous amount of fiber and must be delivered through a larger bore NET or a PEG. Although blenderized formulas are commercially available, patients can be instructed in the preparation of a balanced regimen using blenderized foods from their kitchen.

8] Supplements

Patients who cannot meet all of their protein or calorie needs may be administered supplements. They may take the form of a liquid, shake, pudding, or solid food bar and may be taken with or between meals. The multitude of available products and conflicting information regarding product efficacy can often make appropriate aggressive nutritional support complicated.[3,4]

9] Home Blend Formulas

Home blend formulas are the formulas which are to be prepared in home itself. The patient is required to prepare tube feeding at home.Home blend formulas contain the active ingredients which are taken in combination or alone. Occasionally patient requests or is required to prepare tube feeding at home.

Indications Of Feeding

Tube feeding should be considered for patients who cannot or will not eat, for patients who have a functional gut, and for whom a safe method of access is possible.

1. In most patients, nutrition support should be initiated after 1-2 weeks without nutrient intake. Enteral feeding is preferable to parenteral therapy provided there are no contraindications, access can be attained safely, and oral intake is not possible. In some patients, combinations of enteral and parenteral nutrition may be necessary to meet their nutritional needs.

2. Mechanical obstruction is the only absolute contraindication to enteral feeding.

3. Partial nutritional support used to supplement diet if oral intake is inadequate in conditions such as swallowing impairments due to stroke, Parkinson's disease, motor neuron disease severe weight loss, anorexia and nausea.[5]

Guidelines For Selection Of Product

Substrate Source: Individual requirements and ability to tolerate various sources of intact or elemental carbohydrate protein and fiber.

Calorie Concentration: The calorie to volume ratio will affect the volume required to meet nutritional requirements. Increasing the calorie-to-volume ratio will affect the osmolality of the solution.

Available Feeding Equipment: The size of the feeding tube, drip chamber, and availability of pumps may affect the choice of solution. Blenderized feeding and those containing soy polysaccharide fibers usually require pumps for the infusion through smaller bore tubes due to higher viscosity.

Dosage Types Of Enteral Feeds

The enteral feeds are available in solutions or powdered forms which are required for reconstitution.

A] Solution

Preprepared sterile feeds are used where possible. These are available in 500 ml, 1000 ml, and 1500 ml volumes and come in ready to hang presentation. These sterile feeds can hang for a maximum of 24 hrs. If the feed has to be decanted, avoid hanging times of more than 4 hrs.[8]

Manufacturing Considerations

The basic principles involved in the preparation of homogenous liquids are the solubility of the solute and intermolecular and intermolecular interactions in the final solution at equilibrium are independent of the manner in which the solution is made. The raw materials used in manufacturing liquids should conform to well throughout specifications. These specifications should assure identity, purity, uniformity, and freedom from microbial contamination. Incoming raw materials should be thoroughly tested before they are released for manufacturing. Aside from active ingredients, water is usually the most important constituent in a liquid product. Equipments to be used in processing of sterile products must be scrupulously cleaned. Disinfectant includes dilute solutions of hydrogen peroxide, phenol derivatives and peracetic acid. Equipments can be sterilized using alcohol, boiling water, autoclaving, steam or dry heat.Enteral nutrition products are simple aqueous solutions. So processing is simple, straightforward which involves, use of mixing tanks with agitations and if required steam jacketed for heating and cooling purpose. All materials are formulated on basis of weight per unit volume and water for injection used is delivered to tank, by measuring with metered valves. The sequence of addition of ingredient is very crucial and should be considered, from view of ease of addition, solubility, stability and complexity of analytical procedures followed for in process control. The product is subjected for filtration. Sterilization process is carried by membrane filtration process. The filtration of products or solutions is carried to remove as much as particulate matter at defined size ranges as possible. For processing purpose, factors like water quantity, limit of particles, effective filtration process are important.[9, 10, 11]

B] Powders

Powdered feeds, which require reconstitution are prepared in the diet kitchen and should be used immediately or stored in the fridge.They should be brought back to room temperature before use and used within 24 hrs of mixing.

Manufacturing Considerations

The fundamental manufacturing of powders is Size reduction and Mixing. Size reduction is through titration or pulverisation. Small sized particles are subjected to mixing by using various mixing equipments. The solids or powders are more difficult to subdivide accurately and precisely into individual dose containers or pouches than in liquids.[12]

The tube feeding is of utmost important for enteral nutrition. But, there are some problems associated with tube feeding. The problems and the methods to overcome to this problem are as follows

Difficulty Associated With Tube Feeding

Special problems related to tube feeding include gastroesophageal reflux and aspiration. Tube clogging, dislodgment, and feeding intolerance are also important problems. The incidence of tube clogging from medications or nutrient solutions varies in the literature from 2% to 9% New reclogging catheters are generally successful in alleviating these obstructions, but occasionally a new tube must be placed. Tube dislodgment by either patients or staff can be a considerable problem and account for up to 60% of tube removals. The mean tube life span seems to be 10 days, which underscores the use of these tubes as short-term devices.

Aspiration is one of the most important and controversial complications associated with tube feeding. Issues that need to be considered include the following: (1) Differentiation of aspiration from oropharyngeal or gastric contents, (2) The effect of tube size and presence across upper and lower esophageal sphincters, (3) The effect of body position on gastric reflux and aspiration, (4) The effect of underlying disease (e.g., poor gastric emptying with head trauma or diabetes mellitus), (5) Establishment of gut access for short-term and long-term use, (6) Intermittent vs. continuous feeding regimens, and (7) The possible advantage of jejunostomy feeding over nasogastric or gastrostomy feeding.

Critically ill patients are at risk for diarrhoea from multifactorial etiologies.[3]

The Methods To Overcome This Problem Are Given Below

1] To limit the risk of aspiration during tube feeding, the following should be considered for each patient. For gastric feeding, (A) Raise the head of the bed 30°-45°

during feeding and for 1 hour after, (B) Use intermittent or continuous feeding regimens rather than the rapid bolus method, (C) Check gastric residuals regularly, and (D) Consider jejunal access in patients with recurrent tube feeding (not oropharyngeal) aspiration or in critically ill patients with a higher risk of gastric motility dysfunction (e.g., head trauma). For small bowel feeding, (A) know where the feeding port of the NET or PEJ truly is (the closer to the ligament of Treitz, the better) and (B) episodes of severe vomiting or coughing can displace some nonsurgical tubes, and radiographs may be required to verify current tube position.

2] Concurrent medication use, including sorbitol-based drugs (e.g., Theophylline elixir) and antibiotics, is commonly associated with diarrhoea in the tube-fed population.

3] Fiber probably has little role in controlling tube feeding-related diarrhoea.

4] While metabolic problems may be less frequent with enteral nutrition as compared with parenteral nutrition, careful attention to fluid and electrolyte management can minimize significant metabolic complications.

Precautions For Enteral Nutrition Products

1] Use close feeding containers to decrease risk of organism contamination.

2] Extension tubing administration set and bag should be changed daily.

3] Never add new formula to old formula.

4] Prepared formulas should be refrigerated if not used immediately.

5] Feeding solutions should not be allowed to hang for longer than 8 to 12 hrs.

6] The mean tube life span seems to be 10 days, which underscores the use of these tubes as short term.[3]

QUALITY CONTROL

1] Clarity

Solutions should be free from particulate matter and should be clear. In the case of reconstitution; solution should be clear and sterile after reconstitution.

2] PH

1] Gastric motility is reportedly slowed with solution lower than pH 3.5.

2] The pH level of most commercial formulas is > 3.5.

3] Calorie and nutrient density: gastric emptying time may be slowed by formulas containing higher calorie-nutrient density.[3]

3] Osmolality

It is a function of size and quantity of ionic and molecular particles (protein, carbohydrate, electrolytes, and minerals) within a given volume Unit of measure for osmolality is mOsm/kg of water Vs unit of measure of osmolality mOsm/L.

Factors affecting osmolality are:

a. Minerals/electrolytes: due to dissociation properties and small size
b. Protein: more hydrolyzed components such as amino acids have greater osmotic effect than larger molecular weight component such as intact protein.
c. Carbohydrate: more hydrolyzed components such as glucose have a greater osmotic effect than larger molecular weight such as starch;
d. Formulas with greater hydrolyzed nutrient components have proportionately higher osmolality.[3]

4] Temperature

a. Solution can be administered chilled if they are infused by continuous drip
b. Decreased incidence of GI side effects may occur if intermittent and bolus feedings are allowed to reach room temperature prior to administration.
c. Refrigerated solutions should be brought back to room temperature before use

5] Sterility Test

The sterility testing is of utmost importance in preparation of enteral nutrition products. The products are sterilised by membrane filtration process, and should pass the sterility test.[14]

New Technology In Delivery Of Enteral Nutritional Products

Embrace® Enteral pump with charger

The Ross Embrace® enteral pump is a microprocessor (computer)-controlled pump that provides for accurate, controlled enteral feeding delivery in a safe, user-friendly system. It is a volumetric pump that uses a specially designed feeding set, which includes a cassette that delivers measured amounts of enteral product (1 to 500 ml/hr in 1-ml increments) and features automatic priming of pump set. It can be used in virtually any setting by pediatric and adult patients whenever accurate delivery of enteral nutrition liquids is required. Its small size and weight also make it a great choice for mobile tube-fed patients who take along their enteral pump. An array of optional travel accessories makes tube feeding less intrusive on active lifestyles. Flow rate accuracy is +/- 5% or 0.5 ml/hr, whichever is greater.

SUMMARY

Thus this review mainly deals with the Formulation, Development of enteral nutrition products. Although the types of feeds and the physical characteristics are included, this review mainly emphasizes on formulation aspect of enteral nutrition products. Nutrition may be defined as utilisation of food organisms. Nutrition plays an important role in prevention and management of diseases. Patients unable to consume nutrients orally require alternative form of nutritional support. The term

enteral means "within or by the way of gastrointestinal tract "The different types of enteral nutrition is classified as Short term and Long term enteral nutrition. Short term nutrition is mainly through nasal route. Long term enteral nutrition is for more than 4 weeks and is further classified as gastrostomy and jejunostomy. Enteral tubes are made of PVC, Polyurethane etc. The selection of the enteral formula is patient specific and thus its nutritional requirements, the ingredients used in it are taken into consideration. The classification of formulas is also done on the basis of the patient's needs and ingredients used in it. The enteral feeds can be given in the form of solutions and powders which require reconstitution. The quality control test like Osmolality, pH, Temperature is also taken into consideration. Thus, the purpose here is to point out explicitly the formulation development of enteral nutrition products.

CONCLUSION

It can thus be concluded that the formulation, development of enteral nutrition products is very essential for patients who have an eating or swallowing problem. Proper use of the ingredients in formulation according to patients needs should be done in order to develop an efficient formulation of enteral nutrition.

REFERENCES

1. Satyanarayan U, Chakrapani U. Biochemistry, 3rd ed. Uppala Author publisher Interlinks; 2002.p.535.
2. http://dictionary.webmd.com/terms/enteral accessed on 2009 August 12.
3. http://www.indiandoctors.com/papers/nutri/enteral.htm accessed on 2009 August 16.
4. https://www.healthsystem.virginia.edu/.../nutrition articles/malonearticle.pdf accessed on 2009 September 06.
5. www.nccpeds.com/powerpoints/enteralnutrition.ppt accessed on 2009 September 15.
6. sterimed.tradeindia.com/.../Ryles-Tube.html accessed on 2009 August 12.
7. www.lifelinesupply.co.uk/Gastroenterology.html accessed on 2009 September 18.
8. www.nhsgg.org.uk/content/default.asp?page=s861 accessed on 2009 September 25.
9. Lachman L, Leiberman HA, and Joseph K. The Theory and Practise of Industrial Pharmacy, 3rd ed. Bombay: Varghese Publishing House; 1991. p. 473-475,711-715.
10. Avis KE, Liberman HA, and Lachman L. Pharmaceutical Dosage forms, Parenteral Medication. 2nd ed. Marcel Dekker; 1993.
11. Turo SG. Sterile Dosage Form, Their Preparation and clinical application, 4th ed. Lee and Febiger publisher; 1993.
12. Pawar AP, Gaud RS. Modern Dispensing Pharmacy, 2nd ed. B.I.Publications; 2005. p. 278-279
13. www.rxkinetics.com/tpututorial/2_3.html accessed on 2009 December 23.
14. United States pharmacopoeia. The official compendia of standards, official 2007 May 01.
15. http://en.wikipedia.org/wiki/Feeding_tube accessed on 2009 October 05.
16. www.glucerna.net/en/products_powders.jsp accessed on 2009 October 08.
17. www.answers.com/topic/feeding-tube accessed on 2009 December 14.
18. http://www.abbottstore.com/Ensure+reg/Ensure-Powder-Vanilla-14-oz-container-case- of-6-/invt/00750 accessed on 2009 October 23.

Table 1: Water content of enteral formula for adults.[3]

Caloric density (kcal/ml formula)	Water content (ml/1000 ml formula)	Water content
1.0 – 1.2	800-860	80-86
1.5	760-780	76-78
2.0	690-710	69-71

Table 2: Marketed products and manufacturer of Enteral product.[16, 18]

Sr. No	Product Name	Image of product	Manufacturer	Description
1)	JEVITY® 1 CAL		ROSS PRODUCTS	An isotonic, fiber-fortified, high-nitrogen liquid formula providing complete, balanced nutrition for patients requiring short- or long-term tube feeding. The fiber level helps patients maintain normal bowel function. Because it is isotonic, it reduces the potential for hyperosmotic diarrhoea. For patients requiring acute-care or chronic tube feedings or for patients intolerant to low-residue feedings. Lactose- and glucose-free.
2)	Ensure Plus®	 FLAVOUR: VANILLA	ROSS PRODUCTS	Great source of calories. High in protein to help patient gain or maintain a healthy weight. A complete and balanced oral nutritional supplement that can used with or between meals or in appropriate amount as a meal replacement.

3)	Ensure®	 FLAVOUR: VANILLA	ROSS PRODUCTS	For people who need a low-cholesterol or low-residue diet or patients recovering from illness or surgery. Lactose- and gluten-free. Products containing fiber with FOS helps maintain digestive tract health. 8-fl-oz cans. For supplemental or sole-source nutrition. For oral or tube feeding.
4)	Glucerna®		ROSS PRODUCTS	A reduced carbohydrate, modified fat, fiber-containing formula, designed to enhance blood glucose. Provides only 34.3% of total calories as carbohydrate. Unique fat blend, rich in monounsaturated fatty acids, provides the majority of the nonprotein calories.

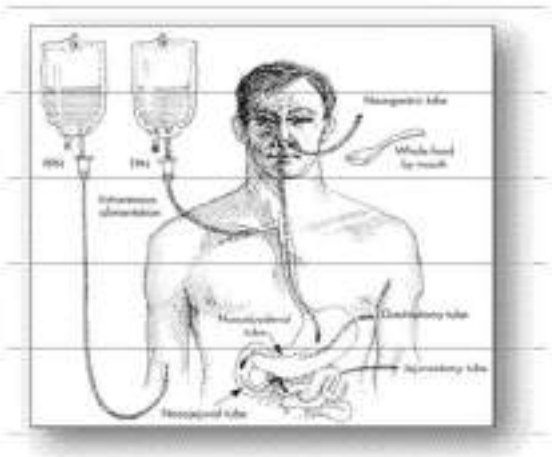

Figure 1: Various types of Enteral nutrition's route of administration

Figure 3: Ryle's tube

Figure 4 : Levin's tube

Figure 2: Classification of enteral nutrition[12, 17]

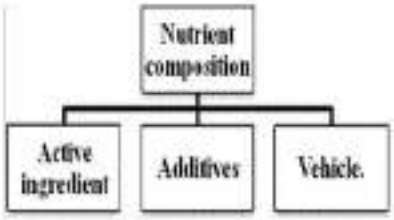

Figure 5: Nutrient compositions