Prospect of Compressed Pellets of Diclofenac and Rantidine as a Single Tablet Dosage Form.

A thesis submitted to the Department of Pharmacy, East West University, Dhaka in partial fulfillment of the requirements for the degree of Bachelor Pharmacy

Submitted By: - Nazia Akhter Chaity

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Department of Pharmacy

East West University

Dedicated to

My dear lovely parent

CERTIFICATE

This is to certify that the thesis "Prospect of compressed pellets of diclofenac and rantidine as a single tablet dosage form," submitted to the Department of Pharmacy, East West University, Dhaka in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (B.Pharm) was carried out by Nazia Akhter Chaity (ID: 2005-3-70-026) under our guidance and supervision and that no part of the thesis has been submitted for any other degree. We further certify that all the sources of information and laboratory facilities availed of this connection is duly acknowledged.

Md. Zakiur Rahman
Lecturer
Department of Pharmacy
East West University
(Supervisor)

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Abstract

Introduction:- Combination dosage forms are gaining approval in global markets in increasing numbers. Combining two or more drugs result in a product that is more effective than its separate components.

Objective: - To investigate the combined effect of diclofenac and ranitidine together as enteric coated pellet form which is compressed into tablet formulation.

Methods: -I this study an innovative formulation have been proposed that includes diclofenac and ranitidine together as enteric coated pellet form which is compressed into tablet formulation.

The literature contains numerous reports and experiments that had been studied on the combination preparation of diclofenac and ranitidine together in a single formulation. If this formulation is prepared it can be effectively use in the therapy of NSAID-induced gastrointestinal disorders and will increase patient compliance.

The method that has been proposed for pellet manufacture is powder layer technique. Initially two individual enteric coated pellets of ranitidine and diclofenac must be made and then they should be compressed together by direct compression method. The proposed formulations are to be evaluated by performing the dissolution and disintegration analysis.

Results: - It is possible to combine diclofenac and ranitidine together as enteric coated pellet form which is then compressed into a tablet.

Conclusions: - Compression of coated pellets is a challenging task necessitating the optimization of various formulations and process variables. In this study how two drugs in pellet form can be presented in a more convenient dosage form has been proposed.

Key words: Combination dosage forms, diclofenac, ranitidine, enteric coating, pellet, powder layer technique and direct compression method.

Introduction

Combination drugs or products also known as fixed dose combinations (FDCs) are combination of two or more active ingredients combined in a single dosage form available in certain fixed doses. Usually, these active drugs come from different classes of drugs (en.wikipedia.org).

Combination therapies are gaining approval in global markets in increasing numbers. Combining two or more entities (by using drugs, biological, and devices) results in a product that is more effective than its separate components. Combination products also known as fixed dose.

The Food and Drug Administration, USA defines a combination product as a product composed of any combination of a drug and a device or a biological product and a device or a drug and a biological product or a drug, device, and a biological product.

Several branded formulations are available in Bangladesh which is either single or fixed dose combination drugs. No doubt all the formulations are meant for prevention or treatment of ailments and diseases, out of which only a few drugs are lifesaving and essential; rest of the drugs are substitutes for each other. The safety of the combination drugs has to be thoroughly evaluated and there are considerations for the drugs that are already in the market as individual or single drug entity. However, the safety profile of the established drugs will alter when they are combined together. There was alarming increase in irrational FDCs in recent years and pharmaceutical companies manufacturing these FDCs are luring physicians to prescribe by unethical means. This may be due to the implementation of product patent regime where the mediocre companies find various alternatives to sustain themselves in the market place and combination products for newer indications play a major role (Sreedhar D., Subramanian G., and Udupa N.).

Today, combination products range from drug-drug combinations to drug-device combinations (such as drug-eluting stents for coronary blockages), to drug-biological

products (such as monoclonal antibodies combined with a chemotherapy agent for the treatment of cancer).

The most common combination, called a fixed-dose combination (FDC), consists of two or more active ingredients that are physically or chemically combined to produce a single tablet. Each product type offers significant solutions to many of the problems plaguing healthcare.

There are many reasons why it is desirable to combine drugs. The main rationale is to produce a better, more beneficial treatment. Another rationale for combining drugs is to simplify treatment regiments for patients. Fixed dose combination drug products may improve medication compliance by reducing the pill burden of patients(Palangio M., Gilder W., Keffer M., Landan C., Morris E., Doyle R., Jiang J., Damask M., and de Padova A., 2000 and Wertheimer A. and Morrison A., 2002).

Pharmaceutical companies are turning toward fixed-dose combination products to diffuse the impact of generic competition, revitalize established brands, fill gaps in product pipelines, and enhance patient compliance. In some instances, the addition of a second compound increases the efficacy of the first. As the cost of drug research continues to climb, the number of new molecular entities submitted for approval to the FDA is decreasing. Drug developers are seeking ways to offset this imbalance. Generally, combinations of established therapies carry low risk but high financial reward because the resulting product comes with new patents that protect it from generic competition.

For the patient, a combination product means a reduction in the number of prescriptions, usually reflecting a cost savings due to fewer co-pays in the case of prescription plans. Taking one pill versus two or more will decrease the complexity of the drug regimen and increase patient compliance. Additionally, while combination therapies have complementary modes of action of the separate ingredients to produce the desired therapeutic effect, the side-effect profiles are not additive.

We look at the history of combination therapies (drug-drug, drug device, and drug-biological), explain FDA guidelines on combination products, discuss how patents play a role in decision making, and examine different approaches the pharmaceutical industry

has taken with regard to combination products and patent extensions. In addition to deciding if the benefits will be worth the risk when creating a combination therapy, the manufacturer has many decisions to make when creating the development plan.

We exhaustively examine combination therapies product development for fixed-dose combinations and drug/device/biological combinations. By working closely with the FDA, a sponsor company can plan and implement the clinical studies necessary for marketing approval as expediently and cost-effectively as possible. Marketplace issues such as labeling, pricing, and managed care involvement are also examined. Finally, examples of each type of combination product are discussed at length(Richard F. and Olivia Scaros).

Combination of Products Introduces Some New Issues (Roger Harrison G., 2005):-

- Drug release from polymer materials
- Local safety issues of drug and polymer
- Drug interaction with new contact materials
- Drug-device interactions
- Stability of the drug with the device
- Sterility for combination products
- Dose dumping from implanted systems, etc.

Advantages of Combination Drug:-

(1) Reduces errors in treatment:-

Doctors use their skill and experience to decide on the optimum treatment for a patient. These efforts are completely wasted if the patient does not take the prescribed drugs as recommended and it has been shown repeatedly and consistently that this failure rate increases with the number of medicaments that have to be taken.

Youth and age may also be minor factors but the percentage of errors in taking prescribed medicines is directly proportional to the complexity of the regimen. The greater the number of items, the greater the risk of medicines not being taken as prescribed.

This has been shown in hospital, in out patients and in general practice, that the need is for increased simplicity of administration rather than for newer and better drugs. As many patients in practice need many drugs at standard dosages, only combinations can give the simplicity needed to cut down errors in treatment.

(2) Reduces risk of drug interaction:-

Whenever a patient is given more than one drug at the same time, there is a possible risk of drug interaction. The mechanisms of interaction are many and varied and it has been rightly pointed out that it is no longer possible for practicing clinicians to be aware of all possible risks. Therefore, as stated by 'every time a physician adds to the number of drugs a patient is taking, he may devise a novel combination that has a special risk'. If additional drugs are needed for the optimum management of the patient, this risk can be avoided by using a combination product, if one is available. With such a product, all the risks of interaction have been taken in experimental laboratories and controlled clinical trials instead of the unsupervised conditions of a patient in his home. A further point, relevant to drug interaction, is that a combination product is three times as likely to be the only medication taken by a patient as single products so that the risk of interaction with other drugs is correspondingly less.

(3) Convenience to doctor and patient:-

Convenience, often dismissed casually as 'mere convenience', is an important aspect of a practical business, such as the prescribing, describing, remembering and taking of medicines.

Doctors have strictly limited time with each patient and their failure in giving clear instructions is recognized as a significant factor in causing errors with more complicated multi-tablet regimens. The greater convenience and the ease of describing the taking of combination products will assist in reducing this source of error. From the point of view of the patient, the easier his medicines are to remember and take the better. Here again, the combination product approaches the ideal for the patient who needs more than one medicament. A further advantage which usually applies is economy, as combination formulations are about 20% cheaper on average than separate ingredients; quite apart

from reduced dispensing, container and similar pharmacy costs(Bootman J., Townsend R. and McGhan W., 1999).

In brief the advantages of Combination drug include:

- Provide a better, more beneficial treatment.
- It simplifies treatment regiments for patients.
- Innovative ways to extend lifecycles of existing products for manufacturer (value added).
- Reduced toxicity in patients
- Fewer side effects for patients
- Higher rate of efficiency
- Improved patient compliance
- Prevention of drug resistance
- Multiple effects for single entity
- Co existing diagnoses

Examples of Combination Drug:-

- NSAIDs-PPI
- Cardiovascular Agents Including Dyslipidemia Combinations
- Antihypertensive Combinations

  -ACE inhibitors-diuretic-calcium channel blockers.
- Antihypertensive/Lipid-Lowering Combinations
- HIV Medications
- Anti-Infective Combination Therapies
- Oral Contraceptives
- Type 2 diabetes (e.g., Glucovance, a combination of glyburide and metformin)

  -Glipizide- metformin hydrochloride

  -Glyburide-metformin hydrochloride

  -Metformin-hydrochloride- rosiglitazone maleate/ sitagliptin

-Metformin- hydrochloride-pioglitazone hydrochloride

-Glimepiride- rosiglitazone maleate

-Glimepiride-pioglitazone hydrochloride

- Hyperlipidemia (e.g., Advicor, a combination of lovastatin and niacin)

  -Ezetimibe-simvastatin and

  -Lovastatin- niacin.

Objectives

The aim of this study is to investigate the combined effect of two drug products, that is, diclofenac and ranitidine together as enteric coated pellet form which is then compressed into a tablet.

Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) taken to reduce inflammation and as an analgesic reducing pain in conditions such as arthritis or acute injury. But one of the major side effects of this drug is gastrointestinal disorders. The development of ulceration, bleeding and/or damage to the gastric mucosa requires immediate termination of treatment with diclofenac.

So patients are given an ulcer-protective drug, ranitidine, to treat these gastrointestinal disorders and also as prophylaxis during long-term treatment of NSAIDs.

It has been reported that ranitidine is able to protect against the ulcerogenic effect of non-steroidal anti-inflammatory agents, this being the reason of combining this two drugs (en.wikipedia.org).

The reasons of combining this two drugs and compressed into a tablet includes: -

• Convenience to doctor and improved patient compliance.

Normally to prevent indigestion, hyperacidity and heartburn associated with consuming food and drink patient takes ranitidine with water half to one hour before eating and then NSAIDs are taken. But now as the two drugs are given together there will be no chance of missed dose. Patient will not have to be concerned of taking ranitidine separately along with diclofenac.

• Reduces errors in treatment. Provide a better, more beneficial treatment.

A patient may forget to take ranitidine which will lead to gastric problems. But now as the two drugs are given together it provides more beneficial treatment reducing toxicity and side effects for patients.

Incompatibility: -

Through literature survey it has been found that in a study of drug–drug interaction between a commercial diclofenac sodium enteric-coated tablet and a ranitidine HCI tablet was evaluated using a dual radiotelemetric technique according to a randomized three-way Latin-Square crossover design balanced for carryover effects. The results of this study indicated that there was no drug–drug interaction between diclofenac and ranitidine (Catherine A. and Robert Blum A.,1993). Food does not interfere with absorption of ranitidine. (www.umm.edu)

Feasibility: -

Through literature survey it has been found that many experiments were performed or studied on the combination preparation of diclofenac and ranitidine together in a single formulation such as the bioavailability of a formulation containing a diclofenac-ranitidine combination was studied where the two agents was developed in a single formulation.

Then the effect of ranitidine in the therapy of NSAID-induced gastroduodenal disorders was studied. Then the release profile of diclofenac sodium from matrix pellet compressed into multiple units pellet system was studied. The feasibility of formulating ranitidine into pellets with a range of alternative excipients in place of microcrystalline cellulose (MCC) was also studied and so on.

But still now ranitidine and diclofenac has not been formulated together in enteric coated pellet compressed tablet form. As literature report verifies that these two drugs can be combined together so we can conclude that it is feasible to prepare diclofenac and ranitidine into pellet and combine them in a single formulation and can use effectively in the therapy of NSAID-induced gastrointestinal disorders.

In this study we have chosen diclofenac and ranitidine for the investigation of the combined effect together as enteric coated pellet form which is then compressed into a tablet, because diclofenac is the most commonly used NSAIDs and is available as OTC drug in Bangladesh and hence it has low price.

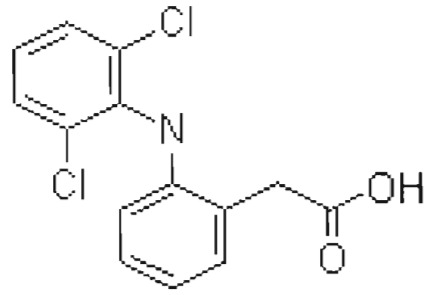


Fig 1:- Structure of Diclofenac

On the other hand we have chosen ranitidine, a H2-receptor antagonist, as it is mostly used in the therapy of NSAID and provides excellent relief of NSAID symptoms. Ranitidine is also available as OTC drug in Bangladesh. Other member of H2-receptor antagonists like famotidine has not been chosen because rantidine provide more beneficial effect in the reduction of gastric acid than famotidine.

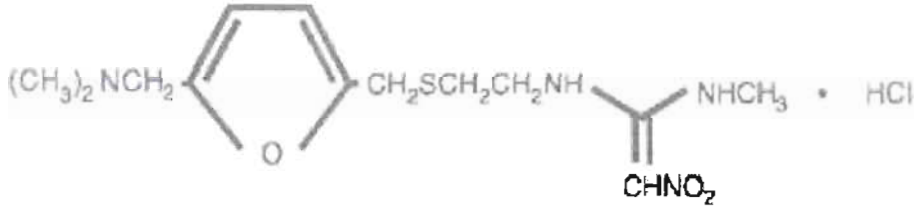


Fig 2:- Structure of Rantidine

Through literature survey it has been found that the effects of ranitidine compared with those of famotidine on the quality of gastric ulcer healing was investigated where it was found that initial therapy with ranitidine significantly improved the quality of gastric ulcer healing and the histological scores of gastric mucosa compared with famotidine (Higuchi K., Watanabe T., Tominaga K., Shiba M., Nakagawa K., Uno H., Kitada K. and Satoh H,1981).

In an early study where the effects of famotidine nocturnal versus ranitidine nocturnal was investigated for the prevention of duodenal ulcer relapse.

The result showed that the efficacy of 20 mg famotidine nocte is comparable to that of ranitidine in preventing duodenal ulcer recurrence, with comparable tolerability for long-term therapy (www3.interscience.wiley.com).

In another early study the effect of high-dose ranitidine was investigated for the prevention of recurrent peptic ulcer disease in rheumatoid arthritis patients taking NSAIDs. The result showed that high dose ranitidine is effective for the prevention of recurrent duodenal ulcer but not for recurrent gastric ulcer in rheumatoid arthritis patients taking NSAIDs (www3.interscience.wiley.com).

Sometimes, in many countries misoprostol is used in the therapy of NSAIDs. Misoprostol is a synthetic analog of prostaglanding E1 (PGE1) that binds to the EPS receptor on parietal cells and inhibits acid secreton, stimulates mucus and bicarbonate secretion, ad increases mucosa blood flow (cytoprotective effect).

Misoprostol agent undergoes extensive first-pass metabolism to the main active metabolite, misoprostol acid. This agent has a half-life of 20-40 minutes, and elimination is mostly renal. Food delay misoprostol absorption.

We did not choose misoprostol in our study due to is short half life, incompatibility with food and many serious adverse effects including worsening of inflammatory bowel disease and miscarriage (www.angelfire.com).

Furthermore, recent studies suggest that bedtime ranitidine 150 or 300 mg is more effective than bedtime omeprazole 20 mg for controlling the nocturnal acid break-through observed in subjects treated with omeprazole 20 mg twice daily.

Low-dose ranitidine 75 mg has been available as over-the-counter medications for a few years and have proved to be effective and safe for self-controlling acid-related symptoms. Results from pharmacodynamic studies have shown that low-dose ranitidine insignificantly more effective for suppressing acid secretion than antacids and placebo even though the onset of action with the low-dose ranitidine is slower than that seen with antacids (Jia-Qing Huang, 2001).

Background

The purpose of this study is to investigate the combined effect of diclofenac enteric coated pellets and rantidine enteric coated pellets when compressed into a single tablet form. The principle of this study is to improve or increase patience compliance.

Non-steroidal anti-inflammatory drugs (NSAIDs) are used to relieve pain and inflammation. NSAIDs are associated with several side effects. The frequency of side effects varies among NSAIDs. The most common side effects are they can occasionally cause serious side effects on the gut, such as ulceration, bleeding or perforation of the stomach or intestinal lining (www.medicinenet.com).

These side effects occur as NSAIDs inhibit the production of protective prostaglandins; the stomach is less protected from acidity. Bleeding in the stomach, as well the intestines occurs with long-term and high dose NSAID use. Then ulcers may follow, or an obstruction in the intestines due to the irritation This side effect can occur without warning at any time during treatment with diclofenac. This type of side effect is more likely to occur in elderly people and in people taking high doses of the medicine. It is important that these people, as well as people with a history of disorders affecting the stomach or intestines, are closely monitored by a doctor while taking this medicine (www.netdoctor.co.uk).

One promising solution to the problem of healing and preventing NSAID associated upper gastrointestinal problems, like ulcers and dyspeptic symptoms in patients needing continuous NSAID treatment, is to avoid contact between the NSAID and acidic gastric juice by delaying the NSAID release or to combine the NSAID treatment with an anti-ulcer drug approved for the healing and/or prophylaxis of NSAID associated gastrointestinal side-effects such as prostaglandin analogues, H2-blockers, and proton pump inhibitors.

In most cases doctors prescribe H2 blockers to prevent and treat peptic ulcers that can occur as a side effect of non-steroidal anti-inflammatory drugs (NSAIDs), such as diclofenac.

Histamine H2 receptor blocking agents are a class of drugs which act as antagonists of the histamine H2 receptor and can effectively inhibit gastric acid secretion. H2 blockers include cimetidine, ranitidine, ebrotidine, pabutidine, lafutidine, loxtidine and famotidine. But ranitidine is mostly given along with diclofenac.

Ranitidine acts in the stomach to decrease the production of stomach acid. It works by blocking histamine H2 receptors that are found on the cells in the stomach lining. Natural body chemical called histamine normally binds to these receptors, causing the cells to produce stomach acid. By blocking the H2 receptors, ranitidine prevents histamine from binding to them. This stops the cells from producing stomach acid.

By reducing the production of stomach acid, ranitidine can be used to treat all these and other conditions. It stops excess acid flowing back into the food pipe and can be used to relieve heartburn symptoms associated with acid reflux. It also allows the oesophagus to heal in reflux oesophagitis. By reducing the amount of acid in the stomach and duodenum ranitidine relieves the symptoms of indigestion. It also allows peptic ulcers to heal, and prevents them from recurring.

Ranitidine is also used to depress stomach acid production in various other conditions. It is used in varying doses and for varying lengths of time depending on the condition being treated (www.tiscali.co.uk).

Now a day diclofenac is given as enteric coated tablet form which has a special 'enteric coating' that is designed to prevent the absorption of the diclofenac in the stomach, and thus reduce the risk of stomach irritation and indigestion. The diclofenac is absorbed when the tablet reaches the intestine (www.netdoctor.co.uk).

But still diclofenac enteric coated tablet may cause gastrointestinal problems. So it is necessary to take rantidine along with diclofenac.

Other reasons for enteric coating:-

- To protect acid-labile drugs from the GI fluid. Eg-Enzymes and certain antibiotics.
- To prevent gastric distress or nausia due to irritation from a drug. Eg -Sodium salicylate.
- To deliver drugs intended for local action in the intestines. Eg- Intestinal antiseptic.
- To deliver drugs that is optimally absorbed in the small intestine.
- To provide a delayed release component for repeat action tablets.

Rantidine is usually given as film coated form in order to mask the drug's bitter taste, to provide protection from destructive environmental elements, and for esthetic purposes. And also to prevent degradation upon aging and that such degradation is accelerated by heat, moisture and light (Franz, Robert M. and Mariner R, 1989).

In this study we have made two individual pellets of diclofenac and rantidine where diclofenac pellet is enteric coated and ranitidine pellet is film coated and then compressed into a tablet shape.

The two drugs are given as enteric coated pellet form because extended release and delayed release dosage forms comprising multiple units such as pellets offer various advantages over single unit dosage forms such as coated tablets and capsules. The major advantages are reduced risk of local irritation and toxicity, less variable bioavailability, reduced inter and intra-individual variations in bioavailability caused for example by food effects, reduced premature drug release from enteric coated dosage forms in the stomach because of a more rapid transit time of coated pellets when compared to enteric coated tablets, and various drug release profiles can be obtained by simply mixing pellets with different release characteristics. Ranitidine is very hygroscopic so it is another reason to give ranitidine in pellet form. Most of these advantages are associated with the uniform distribution of multiparticulates throughout the gastrointestinal tract.

Pellets also offer a more even and predictable distribution and transportation in the gastro-intestinal tract (Murthy Dwibhashyam V.S.N. and Ratna Vijaya J.).

Pellets being more stable than API, have now developed a market for itself. Other advantages of pellet in manufacture's aspect are:-

- Cost reduction due to elimination of Granulation and Lubrication bottle necks.
- Enhance competitiveness and productivity by increasing flexibility in batch size.
- Reduces no. of in process line clearances and quality checks.
- Minimizes blockage of funds as inventory of active and inactive raw material is removed completely.
- Reduction in sampling and analysis of raw materials and finished products.
- Pellets facilitate single delivery for various active ingredients that can be targeted for dissolution in stomach or intestine. This can offer competitive niche and value addition in today's competitive markets.

With respect to the final dosage form, the coated pellets can either be filled into hard gelatin capsules or can be compressed into tablets (www.titanpharma.com).

Mostly tablet formulation is the preferred one because of various advantages associated with it. In our research we have proposed to compress the two pellets into one single tablet because of convenience to patient, physician and pharmacist ease of administration and most importantly accuracy of dosage are among the advantages that have led to the constantly increasing use of medicament-containing compressed tablets. Furthermore, the development of machinery for the high speed, large volume production of uniform tablets has been responsible for their steadily growing importance in the pharmaceutical trade (Guyer Thomas L., Richland M. I., Franz, Otsego M. I. and Robert M, 1986).

The pellets were not filled into capsules as there are some disadvantages such as feasibility of tampering, difficulties in esophageal transport, and higher production costs. Therefore, tablet formulation is the preferred final dosage form. Only a few multiple unit containing tablet products are available.

This is due to the inherent challenges involved in the compression of coated pellets. Ideally, the compacted pellets should disintegrate rapidly into individual pellets in gastrointestinal fluids and the drug release pattern of the coated pellets should not be affected by the compression compress. Certain formulation and process parameters play an important role in successful production and functioning of the multiple unit-containing tablets (Dey N. S., Majumdar S. and Rao MEB., 2008).

Methodology

In pharmaceutical industry, pellets can be defined as small, free flowing, spherical particulates manufactured by the agglomeration of fine powders or granules of drug substances and excipients using appropriate processing equipment.

Pellets offer a high degree of flexibility in the design and development of oral dosage forms. They can be divided into desired dose strengths without formulation or process changes and also can be blended to deliver incompatible bioactive agents simultaneously and/or to provide different release profiles at the same or different sites in the gastrointestinal tract. In addition, pellets, taken orally, disperse freely in the GI tract, maximize drug absorption, minimize local irritation of the mucosa by certain irritant drugs and reduce inter and intrapatient variability.

The industrial processes used to create pellets are done by pelletizing techniques. Pelletizing is the process of compressed or molding of product into the shape of a pellet. There are various pelletization techniques but the main purpose of the process is to form a core element containing an active ingredient. The core elements may be coated with agents such as pharmaceutically acceptable polymers to form pellets

The pellet is then coated with at least two enteric layers comprising of enteric polymers and plasticizer either coated on the core or on the separating layer to obtain enteric coated pellets. The core elements or pellets may then be filled directly into hard gelatin capsules or alternatively combined with suitable binders and other tablet excipients and compressed to form tablets.

The most commonly used and intensely investigated pelletization processes are powder layering, solution/suspension layering, extrusion-sphereronization and microencapsulation (James Swarbrick and James Boylan C).

The size of the pellets depends, of course, on the desired size of the pellet to be manufactured. In general, pellets can be as small as 0.I mm, or as large as 2 mm.

Preferred beads are from about 0.3 to about 0.8 mm, in order to provide finished pellets in the desired preferred size range of from about 0.5 to about 1.5 mm in diameter.

It is always preferred for the beads to be of a reasonably narrow particle size distribution, in order to improve the uniformity of the various coatings to be added and the homogeneity of the final product. For example, the beads may be specified as being of particle size ranges such as from 18 to 20 U.S. meshes, from 20 to 25 U.S. mesh, or from 25 to 35 U.S. mesh to obtain acceptable size distributions of various absolute sizes.

The amount of beads to be used obviously depends on the weights and thicknesses of the added layers; in general, the beads comprise from about 15 to about 70 percent of the product. More preferably, the charge of beads represents from about 20 to about 65 percent of the product. (Anderson, Neil R, Oren, Peter L, Ogura, Fujii and Toshiro, 1996)

General Preparation of Core:-

A core for the preparation of enteric coated pellets is prepared by applying layer comprising active ingredient on inert seeds. Such inert seeds are conventionally used in pharmaceutical industry and are generally made of sugar and starch. However, other ingredients such as microcrystalline cellulose (MCC), carbohydrates, cellulose, resins, wax, different oxides and other materials may also be used for the preparation of inert seeds. The seeds are of about 100 to 710 microns, preferably about 150 to 600 microns, more preferably about 200 to 450 microns. The inert seed is generally about 7.5 to 60% by weight of the enteric coated pellets.

The process involves deposition of layer comprising active ingredient, binder and optionally other pharmaceutically acceptable ingredients on the inert seeds. The application of layer comprising active ingredient can be done simultaneous with binder or alternating with binder.

When suspension layering method is employed, the active ingredient and binder are dispersed and/or dissolved in a suitable solvent to which other pharmaceutical ingredient(s) is added. The resulting dispersion is sprayed on inert seeds to obtain core comprising active ingredient.

In this study the method that has been proposed is "powder layering" by which the diclofenac and ranitidine pellet were made.

Powder layering involves the deposition of successive layers of dry powder of drug or excipients or both on preformed nuclei or cores with the help of a binding liquid. Because powder layering involves the simultaneous application of the binding liquid and dry powder, it generally requires specialized equipment. The primary equipment-related requirement in a powder-layering process is that the product container should have solid walls with no perforations to avoid powder loss beneath the product chamber before the powder is picked up by the wet mass of pellets that is being layered on. (Fig 3) The powder layering technique requires specialized equipment such as a rotary-tangential fluidized bed or modified rotating pans (www.glatt.com).

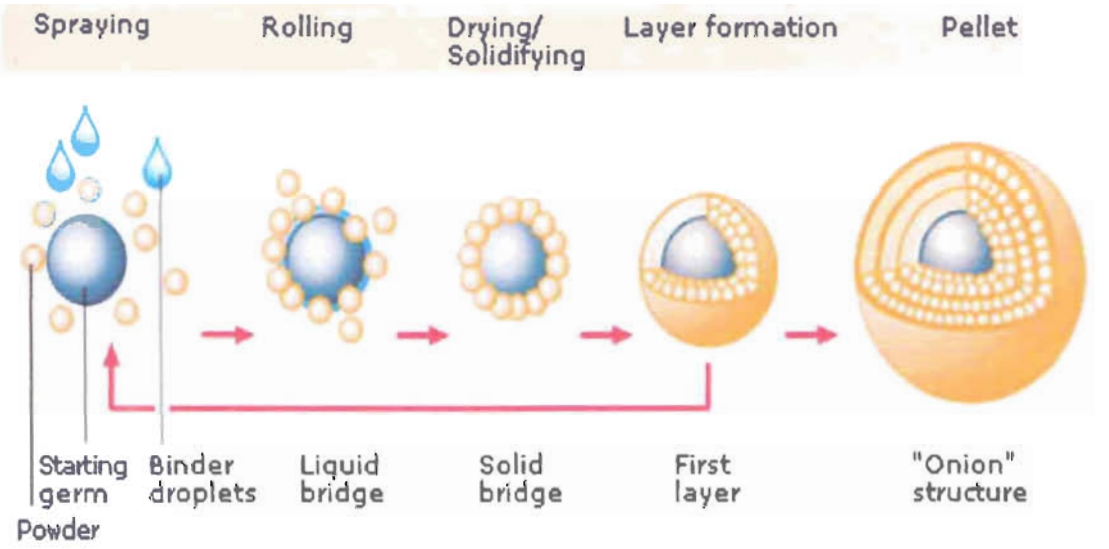


Fig 3:- Principle of the powder layering process.

In this method diclofenac drug powder are charged onto the rotor disk and moved by the spinning of the disk and the air flow through the gap at the wall of the process vessel. Powder and binder liquid is sprayed tangentially into this bed of material. The powder is tolled up to the seeds; the rolling movement ensures spherical particles. The air flow at the wall is drying the pellets - allowing for more binder liquid. It also is possible to add several layers of powder onto the seeds within one batch.

After building the first layer the pellets are dried and the next layer is added with its specific binder. And at the end the pellet is enteric-coating with hydroxypropylmethyl cellulose by a fluidized bed technique.

In the similar way ranitidine pellet was made but at the end the pellet was film coated with hydroxypropylmethyl cellulose by a fluidized bed technique. (Amit Krishna, Antarkar Sunil, Beharilal Jaiswal, Maya Janak Shah and Abdul Shajahan)

After pellet formation two enteric layers comprising of enteric polymers and plasticizer either coated on the core or on the separating layer to obtain enteric coated pellets and different amounts of excipients were blended with coated pellets and then it is compressed into tablet form.

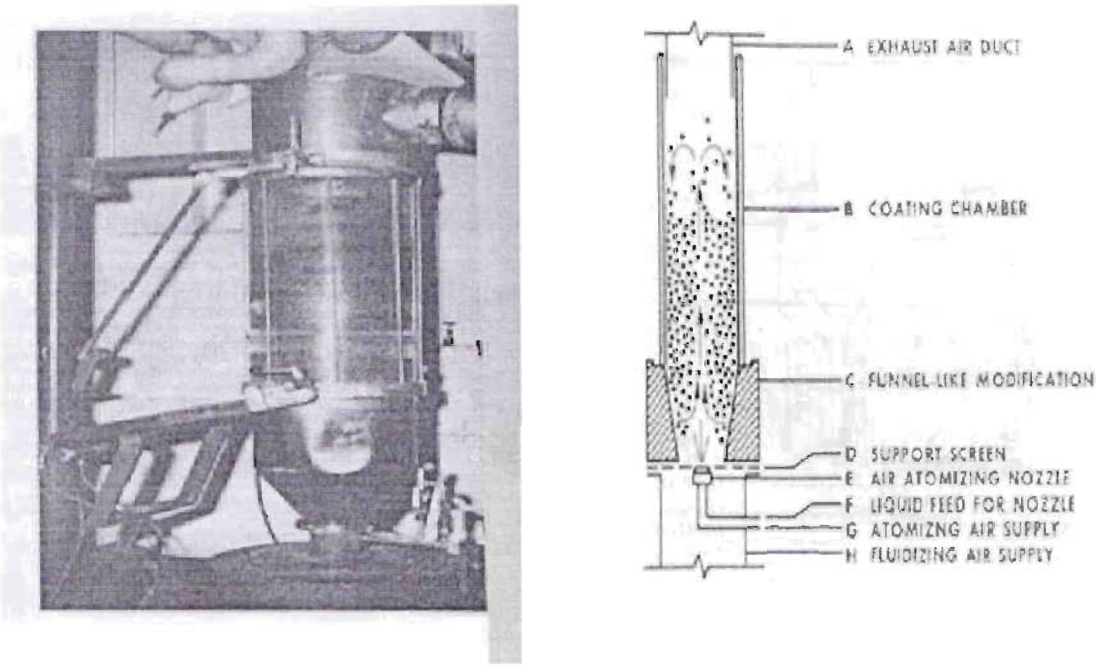
The enteric layer is comprised of an enteric polymer, which must be chosen for compatibility with ranitidine and diclofenac pellet. (Fig 4)

Fig 4:- Layered pellet

The polymer must be one having only a small number of carboxylic acid groups per unit weight or repeating unit of the polymer. The preferred enteric polymer is hydroxypropylmethylcellulose acetate succinate (HPMCAS), which product is defined as containing not less than 4% and not more than 28% of succinoyl groups, which are the only free carboxylic groups in the compound.

Application of the enteric layer to the pellets can be done by various methods and equipments such as fluidized bed coater, standard coating pan and perforated coating pan.

In this study fluidized bed coater technique has been proposed with simultaneous spraying of enteric polymer solution or suspension and warm air drying. Temperature of the drying air and the temperature of the circulating mass of pellets should be kept in the ranges advised by the manufacturer of the enteric polymer.



(a) **(b)**

Fig 5:- Diagram of Fluidized Bed Coater

In fluidization, a gas or liquid is passed through a bed of solid particles which is supported on a perforated or porous plate. In the case of fluidized bed coating, air is passed through a bed of polymer particles. When the frictional force acting on the particles, or pressure drop, of the flowing air through the bed equals or exceeds the weight of the bed, the powder particles become suspended and the bed exhibits liquid-like behavior.

As shown in the figure below, at gas flow rates less than the fluidization velocity, the bed is a fixed bed and there is no movement of particles. At flow rates above minimum fluidization the bed expands and bubbles appear. (Fig 6)

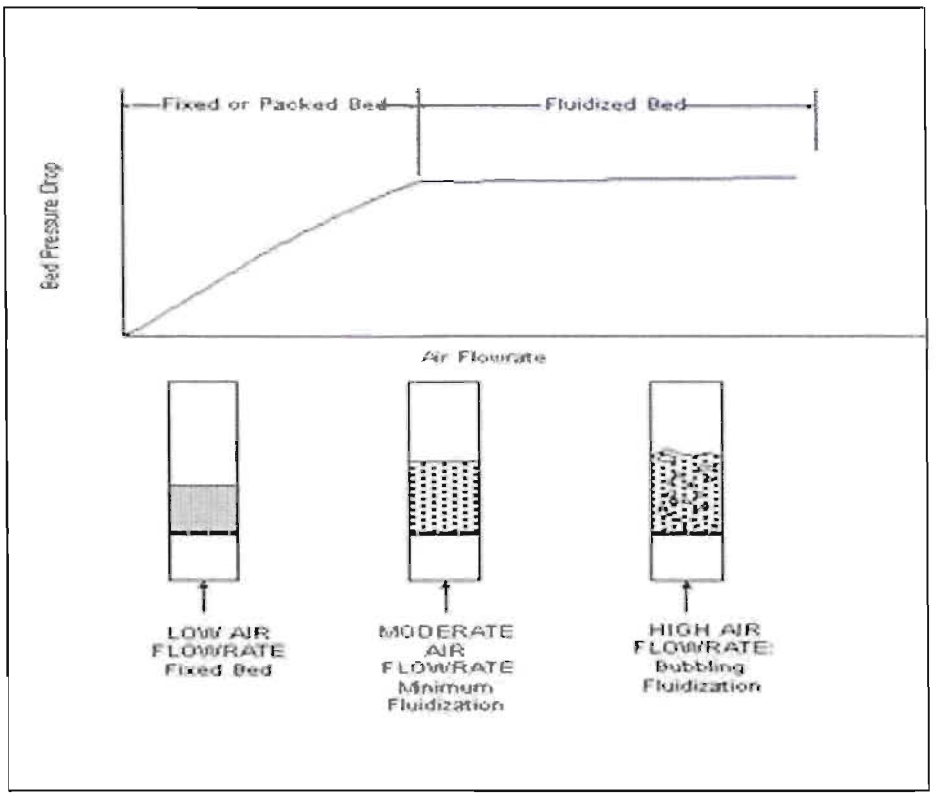


Fig 6:- Fluidization Regimes

The air velocity corresponding to a pressure drop that just equals the weight of the bed is referred to as the minimum fluidization velocity. At this air velocity or flow rate all of the bed particles are completely suspended by the air stream. For a given system, minimum fluidization velocity can be determined from a pressure drop vs. air velocity diagram.

As air flow is increased above the minimum fluidization velocity, the bed may exhibit behaviors ranging from smooth fluidization to bubbling fluidization to dilute fluidization in which powder can be transported by the air stream. Smooth fluidization is desirable for optimal performance in the powder coating process.

The liquid-like nature of the fluidized powder bed allows a metal object to easily be dipped into it. The metal object is preheated to a temperature above the melting point of the polymer prior to being dipped. Powder particles contact and fuse to the hot surface of the object when it enters the bed. Heat is transferred from the object to the polymer, causing the polymer to melt and flow to form a continuous layer. It is then allowed to cool. The coating may be reheated to achieve a smoother finish. For a given object, the thickness of the coating is dependent on two process variables; preheat temperature of the object, and the amount of time for which it is submersed in the powder bed. The thickness of the enteric coating layer in the inventive method is usually in the range from 0.01 to 0.20 mm to ensure satisfactory entero-solubility (Robert P., Hesketh C., Stewart Slater and Michael Carney).

It is also possible to include an opacifying agent in the enteric layer, in the present case as ranitidine is light sensitive so opacifying agent has been used. The most efficient and commonly used opacifiers in pharmaceutical science are the finely powdered oxides of titanium and iron. Amounts of opacifier in the range up to as much as 15% of the product weight, preferably in the range from about 2% to about 10%, will certainly increase the pharmaceutical elegance of the pellets and are likely to improve further the product's stability.

In the present case no finishing layer has been used. A finishing layer over the enteric layer is not necessary in every case, but frequently improves the elegance of the product and its handling, storage and machine ability and may provide further benefits as well. The simplest finishing layer is simply a small amount, about less than 1% of an anti-static ingredient such as talc or silicon dioxide, simply dusted on the surface of the pellets.

Another simple finishing layer is a small amount, about 1%, of a wax such as beeswax melted onto the circulating mass of pellets to further smooth the pellets, reduce static charge, prevent any tendency for pellets to stick together, and increase the hydrophobicity of the surface. More complex finishing layers may constitute a final sprayed-on layer of ingredients.

For example, a thin layer of polymeric material such as hydroxypropylmethylcellulose, polyvinylpyrrolidone and the like, in an amount such as from a few tenths of 1% up to about 3%, may be applied. The polymeric material may also carry a suspension of an opacifier, a bulking agent such as talc, or a coloring material, particularly an opaque finely divided color agent such as red or yellow iron oxide. Such a layer quickly dissolves away in the stomach, leaving the enteric layer to protect the drugs, but provides an added measure of pharmaceutical elegance and protection from mechanical damage to the product.

Finishing layers to be applied to the present product are of essentially the same types commonly used in pharmaceutical science to smooth, seal and color enteric products, and may be formulated and applied in the usual manners (Anderson Neil R, Oren Peter L, Ogura Fujii and Toshiro, 1996).

After enteric coated pellets have been produced it is then compressed into tablet form. However, compression of coated pellets is a challenging task necessitating the optimization of various formulation and process variables. The key formulation variables include composition, porosity, size, shape and density of the pellets; type and amount of polymer coating; nature, size and amount of tableting excipients.

The pellet core should be strong with some degree of plasticity. It should be highly porous, small, with an irregular shape. The critical density to achieve prolonged release was reported to lie between 2.4 and 2.8 g/cm 3. Acrylic polymer films are more flexible and more suitable for the coating of pellets to be compressed into tablets. Thicker coatings offer better resistance to frictional forces.

Solvent based coatings are more flexible and have a higher degree of mechanical stability than the aqueous based ones. The tableting excipients should have cushioning property.

They should not be significantly different in size and density from those of the pellet cores in order to avoid segregation. Addition of 30%-60% of tableting excipients is necessary to avoid any damage to the polymer coat and to retain its functional property (Murthy Dwibhashyam V.S.N., J Vijaya Ratna, 2008).

Coated pellets are usually compressed by direct compression (tablets are compressed directly from powder blends of the active ingredient and suitable excipients) method where the compression is done by single punch machine. A single-punch tablet press makes one tablet at a time. (Fig 8) A "punch" has two pieces of casted tubular metal. The bottom metal piece has a small cavity in one end of the tube; the top metal piece has one end that is tapered into a small rod that will just fit into the small cavity in the other piece. (Fig 7) The rod does not go all the way to the bottom of the cavity, but leaves a small gap. The punch is fitted into a press so that when the handle is depressed and released, the rod goes into and then comes out of the bottom piece. To make a tablet, the pellets and suitable excipients is placed into the bottom piece, and the handle is depressed and released. The powders are compressed and occupy the size of the gap designed in the punch (Stefan Lukas, 1986).

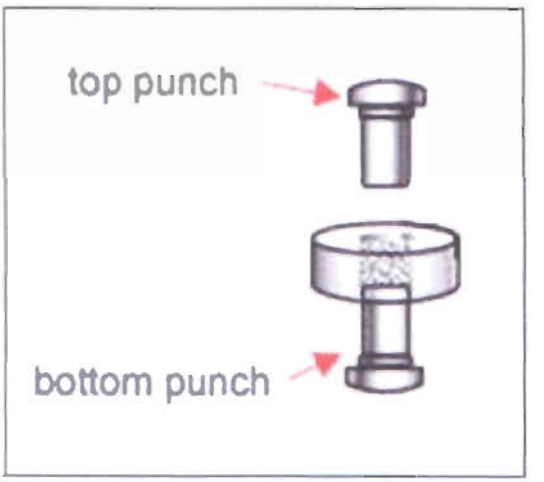


Fig 7:- Tablet Punch

The hardness of the compressed solid dosage form is greater for a given compression force than an equivalent solid dosage form in which the pellets have been treated with talc.

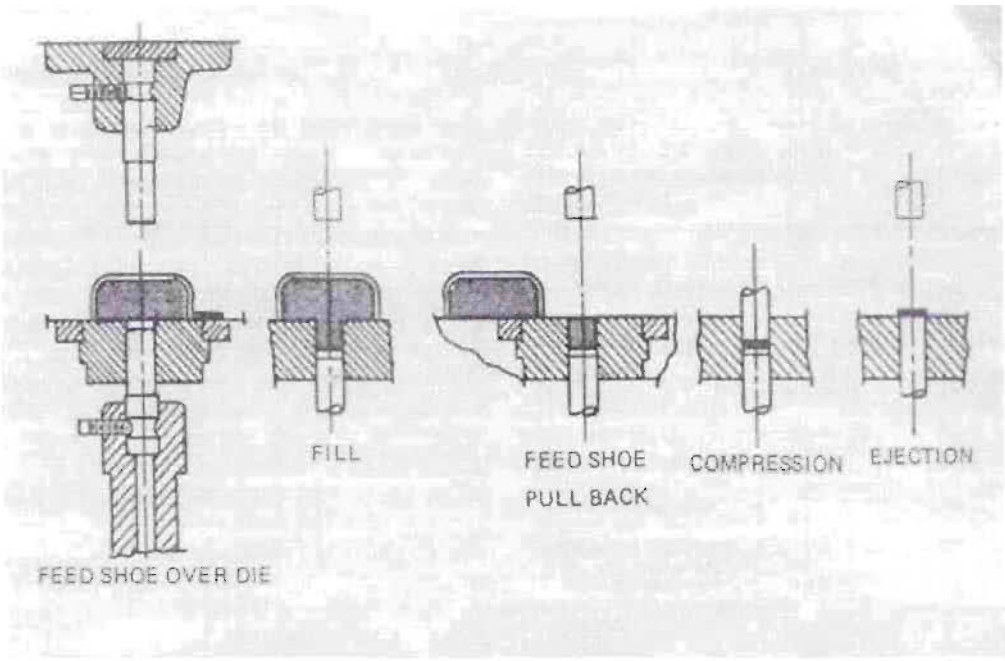


Fig 8:- The compression cycle of a single punch tablet press

It has found that the compressibility of a blend of core elements or pellets and excipients can be significantly affected depending on the choice of antistatic agent. Compressibility is defined herein as the relationship between the force applied during compression in a tablet press and the hardness (or breaking strength) of the resultant tablet. High compressibility is when high tablet hardness can be attained with comparatively low to moderate compression forces. It will be appreciated that the higher the compression force used in tablet formation, the more likely it is that the release of the active agent from the pellet will be adversely affected and/or any coating on the pellet may be fractured. For this reason, lower compression forces (i.e. high compressibility) are favored. Preferably, the compression force at which the solid dosage form is formed is less than 40 kilo newtons. The tabletting can take place with compressive forces in the range from 5 to 40 kN, preferably 10-20 kN (Beckert Thomas, Petereit, Hans-ulrich, Jennifer, Rudolph and Markus, 2005).

The proper formulation of a tablet involves balancing the need for content uniformity (i.e. making sure the same number of core elements or pellets is present in each tablet and therefore the same amount of active ingredient is present in each tablet) and the friability

of any tablet that is formed as well as protection of coated pellets from fracture of the coating during the tabletting step. In this respect, if the weight ratio of core elements or pellets to excipients is too low, there will be problems with content uniformity, while if the weight ratio of core elements or pellets is too high there will not be enough tabletting excipients to cushion the core elements or pellets during compression into a tablet and the structural integrity of the core elements or pellets could be compromised. Also, if the amount of excipients is low the core elements or pellets are more likely to be damaged during compression and the tablets will also be weak and friable because they will not have sufficient binder to hold them together. Therefore the percentage of core elements or pellets in each tablet is ideally in the range of 20 to 50% (more preferably 25 to 35%, but most preferably about 30%) by weight of the total dosage weight.

The size of enteric coated pellets for compression should be less than 850 microns, preferably about 250 to 710 microns, more preferably about 300 to 600 microns and most preferably about 425 to 600 microns The shape and dimension of the tablets has no impact but circular tablets of 5 mm to 20 mm are preferred. The compressed tablets have hardness from 1 kp to 20 kp. (Amit Krishna Antarkar , Sunil Beharilal Jaiswal, Maya Janak Shah and Abdul Shajahan).

The pellets are not directly compressed into tablet, different amounts of excipients were blended with coated pellets and then it is compressed into tablet form. Several excipients have to be used to assist the compaction process and to prevent the rupture and damage of the coated pellets during compression.

The Role of Cushioning Excipients:-

A different approach for protection that has been investigated is the layering of cushioning agents as extra coating layers to the reservoir pellets.

The use of cushioning excipients is an important strategy that can be followed to avoid or minimize damage to the coating of tableted pellets.

Often, tablet disintegration is also improved. These excipients can be used either as powder, granules or pellets. In some applications, they can be incorporated as additional coatings to the heads so forming multilayered head formulations.

The best cushioning effect can be obtained with the following composition of low yield pressure excipients: microcrystalline cellulose, polyethylene glycol 3350 (25%), povidone (25%).

In relation to the cushioning excipients, the crushing strength of the coated pellets is crucial.

Soft pellets can be deformed more easily than hard pellets. It is important that the drug coated pellets have sufficiently crushing strength to avoid critical (Larry Augsburger L. and Stephen W. Hoag)

Procedures of Evaluating Formulations

Tablet properties such as crushing strength friability, weight uniformity, hardness test, dissolution test and disintegration test are checked after the final product has been made.

In vitro tests should be designed to predict how the dosage form will behave in vivo. So in this study we recommend that disintegration and dissolution tests should be routinely used for in vitro testing of enteric-coated dosage forms as these tests are useful during formulation development, as routine quality-control release tests, and for monitoring the physical stability of the dosage form.

Specifications for dissolution testing:-

The dissolution test as defined in the United States Pharmacopoeia (1) is used in judging the quality of pharmaceutical products. Dissolution testing is a method for evaluating physiological availability that depends upon having the drug in a dissolved state

The specifications for drug releases should be established for quality control of prolonged release dosage forms. Basically, it is desirable to employ the release tests which can predict the blood level profile of the drug as precisely as possible. It is also desirable to set the specification including sampling time and amount of drug to be released so as to show the release profile as accurately as possible. The tolerable range of the drug release change depending on the effect of the release rate on absorption or a related pharmacodynamic property (therapeutic window, toxicity or adverse reactions). Therefore, based on the relation between release rate and blood concentration or pharmacological effects, the tolerable range should be set within limits which do not allow great changes in blood concentrations or in clinical efficacy. The narrow tolerance limits should be set as much as possible to decrease the variation in drug release which will provide stable clinical effects.

If the relation between the release rate and blood concentration is not clear, or if sufficient data are not available to prove the correlation, it is difficult to set rational specification. In such a case it is desirable to set specifications using the second method (paddle method) in the Japanese Pharmacopoeia at sampling time points of 20-40%, 40-60%, and more than 70% of the labeled amount of the active ingredient is released.

If 100 rpm and 900 ml of test fluid were used for the paddle method, the tolerance ranges at 1st, 2nd and 3rd points should be set within 15% and 10% of the average release respectively. At the 3rd sample point, only lower limit is acceptable instead of the tolerance range. The acceptance criteria of the drug release follow the criteria of dissolution or release tests of or USP XXI (Carlos Saccone D., Julio Tessorel, Silvino Olivera A. and Nora S. Meneces).

Dissolution Test for Diclofenac :-

Proceed as directed for Procedure for Method B under Apparatus 1 and Apparatus 2, Delayed-Release Dosage Forms.

Acid Stage:-

Medium: - 0.1 N hydrochloric acid; 900 mL

Apparatus 2 (paddles constructed of or coated with, polytef being used): - 50 rpm.

Procedure:-At the end of 2 hours, remove each tablet or the major portion thereof if the Tablet is not intact, from the individual vessels, and subject them to the test in the buffer stage. To the 0.1 N hydrochloric acid remaining in each vessel add 20.0 mL of 5 N sodium hydroxide, and stir for 5 minutes. Determine the amount of C, $H_{11}C_{12}NNaO$, dissolved from UV absorbances at the wavelength of maximum absorbance at about 276 nm on filtered portions of the solution under test in comparison with a Standard solution prepared as follows. Transfer about 68 mg of USP Diclofenac Sodium RS, accurately weighed, to a 100-mL volumetric flask, add 10.0 mL of 0.1 N sodium hydroxide, dilute with water to volume, and mix. Transfer 2.0 mL of this solution to a second 100-mL volumetric flask, dilute with a mixture of 0.1 N hydrochloric acid and 5 N sodium hydroxide (900:20) to volume, and mix. This standard solution contains about 13.6 pg of USP Diclofenac Sodium RS per mL.

Buffer Stage:-

pH 6.8 Phosphate buffer: - Dissolve 76 g of tribasic sodium phosphate in water to obtain 1000 mL of solution.

Mix 250 mL of this solution with 750 mL of 0.1 N hydrochloric acid, and, if necessary, adjust with 2 N hydrochloric acid or 2 N sodium hydroxide to a pH of 6.8 ± 0.05.

Medium: - pH 6.8 Phosphate buffer; 900 mL.
Apparatus: - 2: 50 rpm.

Procedure: - At the end of 45 minutes, determine the amount of C, $H_{11}C_{12}NNaO_2$dissolved from UV absorbances at the wavelength of maximum absorbance at about 276 nm on filtered portions of the solutions under test, suitably diluted with medium, in comparison with a standard solution prepared as follows.

Transfer about 68 mg of USP Diclofenac Sodium RS, accurately weighed, to a 100-mL volumetric flask, add 10.0 mL of 0.1 N sodium hydroxide, dilute with water to volume, and mix. Transfer 2.0 mL of this solution to a second 100-mL volumetric flask, dilute with medium, as obtained in the buffer stage, to volume, and mix. This standard solution contains about 0.02 mg of USP Diclofenac Sodium RS per mL.

Tolerances: - Not less than 75% (Q) of the labeled amount of $CH_{11}C_{12}NNaO_2$, is dissolved

Assay:-pH 2.5 Phosphate buffer— Mix equal volumes of 0.01 M phosphoric acid and 0.01 M monobasic sodium phosphate. If necessary, adjust with additional portions of the appropriate component to a pH of 2.5 ± 0.2.

Mobile phase: - Prepare a filtered and degassed mixture of methanol and pH 2.5 Phosphate buffers (700-300). Adjustments should be made if necessary. [Note-Increasing the proportion of buffer increases resolution].

Diluent: - Prepare a mixture of methanol and water (70:30).
Standard preparation: - Prepare a solution of USP Diclofenac Sodium RS in diluent having a known concentration of about 0.75 mg per mL.

Resolution solution: -Prepare a solution in diluent containing 20 pg of diethyl phthalate, 7.5 pg of USP Diclofenac Related Compound a RS, and 0.75 mg of USP Diclofenac Sodium RS per mL.

Assay preparation:-Transfer 20 tablets to a volumetric flask of such capacity that when filled to volume, a concentration of about 0.75 mg of diclofenac sodium per mL is obtained. Add diluent to about 70% of the capacity of the flask, and shake by mechanical means for not less than 30 minutes to disintegrate the Tablets. Cool to room temperature, dilute with diluent to volume and mix. Pass a portion of the solution through a filter having a 0.5-pm or finer porosity and use the filtrate as the assay preparation (http://www.usp.org).

Dissolution Test for Ranitidine:-

Medium: - Water; 900 mL.

Apparatus: - 2: 50 rpm.

Time: - 45 minutes.

Procedure: -Determine the amount of $C_3H_{22}N_{40}S$ dissolved from UV absorbances at the wavelength of maximum absorbance at about 314 nm using filtered portions of the solution under test, suitably diluted with water, if necessary, in comparison with a standard solution having a known concentration of USP Ranitidine Hydrochloride RS in the same medium.

Tolerances:-Not less than 80% (Q) of the labeled amount of $CH_{22}N_{40}IS$ is dissolved in 45 minutes.

Assay:-Mobile phase, standard preparation, resolution solution, and chromatographic system must be prepared as directed in the assay under ranitidine hydrochloride.

Assay preparation: -Transfer 10 tablets to a minimum of 250 mL of mobile phase, accurately measured. Shake the mixture until the tablets have disintegrated completely, and filter. Dilute the filtrate quantitatively and stepwise if necessary, with mobile phase to obtain a solution having a concentration of ranitidine similar to that of the standard preparation.

Procedures: - Separately inject equal volumes (about 10 pL) of the standard preparation and the assay preparation into the chromatograph, record the chromatograms, and measure the area responses for the major peaks. Calculate the quantity, in mg, of $C_3H_{22}NI0_3S$ in the portion of tablets taken by the formule: - 314.40 / 350.87) (L / D)(C)(r, / rs) in which 314.40 and 350.87 are the molecular weights of ranitidine and ranitidine hydrochloride, respectively; L is the labeled amount, in mg, of ranitidine in each tablet; D is the concentration, in mg per mL, of ranitidine in the Assay preparation, based on the labeled quantity per tablet and the extent of dilution; C is the concentration, in mg per mL, of USP Ranitidine Hydrochloride RS in the Standard preparation; and r, and rs are the peak area responses obtained from the Assay preparation and the Standard preparation, respectively.

Dissolution Test for Delayed Release (enteric coated) Tablets: -

The USP drug-release test for enteric-coated articles appeared in USP XXI in 1985 1431. Either USP dissolution apparatus Type I or II may be used, unless otherwise specified in the individual monograph. Two methods are described, differing in the way that the dissolution media are chanced. In Method A, the tablets are exposed to 750mL of 0. 1N HCI for 2 h and the amount of drug released is determined by assaying an aliquot of the solution. The product passes this portion of the test if the results conform to the acceptance limits shown in table 2. Then 250 mL 0.20M tribasic sodium phosphates are added to the medium, and the pH is adjusted to 6.8. The apparatus is operated for 45 min unless otherwise specified in the individual monograph. An aliquot is removed, and the amount of drug released is determined. The product passes the test if the criteria given in Table 3 are met.In Method B, 1000mL of 0.1N HCI are used, and the acidic medium is replaced entirely with it pH of 6.8 sodium phosphate buffer after 2 h. The product must meet the criteria shown in Tables 2 and 3 (James Swarbrick and James Boylan C).

TABLE 2 USP Acceptance Limits for Dissolution in 0.1N HCl

Stage	Number Tested	Criteria
A1	6	No individual value exceeds 10% dissolved
A2	6	Average of 12 units (A1 + A2) is not more than 10% dissolved, and no individual unit is greater than 25% dissolved
A3	12	Average of 24 units (A1 + A2 + A3) is not more than 10% dissolved, and no individual unit is greater than 25% dissolved

TABLE 3 USP Acceptance Limits for Dissolution in pH 6.8 Phosphate Buffer

Stage	Number Tested	Criteria
B1	6	Each unit is not less than Q + 5%
B2	6	Average of 12 units (B1 + B2) is equal to or greater than Q, and not more than 2 units are less than Q-15% dissolved
B3	12	Average of 24 units (B1 + B2 + B3) is equal to, or greater than, Q and not more than 2 units are less than Q-15%

*Q is the amount of dissolved active in the ingredient specified in the individual monograph, expressed as a percentage of the labeled content.

Specifications for disintegration testing : -

A variety of disintegration test methods for enteric-coated dosage forms have been described in the literature, the earliest by Ioplis in 1915. The most widely used are the United States Pharmacopeia (USP) and British Pharmacopoeia (BP) methods. The USP disintegration test for enteric-coated tablets first appeared in 1955 in USP XV 1411. It was modified in the second supplement to USP XV and has since remained unchanged. The test specifies that one tablet is added to cacti of the six tubes in the USP disintegration apparatus. The apparatus is operated without disks, using simulated gastric fluid (pit 1.2) at 37° C for I h. The tablets are then removed and must show no evidence of disintegration, cracking, or softening. Disks are then added, and the apparatus is operated using simulated intestinal fluid (pit 7.5) at 37°C for period of time equal to 2 h plus the time limit specified in the monograph for uncoated tablets.

The product passes the test if all tablets have disintegrated. If one or two tablets fail to disintegrate completely, 12 additional tablets are tested, and at least I6 of the 18 tablets tested must disintegrate.

The BP disintegration test uses the same apparatus as specified in the USP; however, 0.1N HC1 and pH 6.8 mixed phosphate buffer are used instead of simulated gastric and intestinal fluids. The tablets are exposed to the 11 HCI for 2h and must show no signs of disintegration, apart from fragments of coating, or cracks that would allow the escape of the contents. The fluid is then replaced with the phosphate buffer, and the apparatus is operated with disks for 60 min. The product passes the test if all six tablets have disintegrated.

The test is provided to determine compliance with the limits on disintegration stated in the individual monographs except where the label states that the tablets or capsules are intended for use as troches or are to be chewed or are designed as modified release dosage forms. Determine the type of units under test from the labeling and from observation, and apply the appropriate procedure to 6 or more dosage units. For the purposes of this test, disintegration does not imply complete solution of the unit or even of its active constituent.

Complete disintegration is defined as that state in which any residue of the unit except fragments of insoluble coating or capsule shell remaining on the screen of the test apparatus is a soft mass having no palpably firm core.

Test for delayed release (enteric coated) tablets: -

Place 1 tablet in each of the six tubes of the basket and, if the tablet has a soluble external coating, immerse the basket in water at room temperature for 5 minutes. Then operate the apparatus using simulated gastric fluid TS maintained at 37+28 as the immersion fluid. After 1 hour of operation in simulated gastric fluid TS, lift the basket from the fluid, and observe the tablets: the tablets show no evidence of disintegration, cracking, or softening. Operate the apparatus, using simulated intestinal fluid TS maintained at 37+28 as the immersion fluid, for the time specified in the monograph. Lift the basket from the fluid, and observe the tablets: all of the tablets disintegrate completely. If 1 or 2 tablets fail to

disintegrate completely, repeat the test on 12 additional tablets: not less than 16 of the total of 18 tablets tested disintegrate completely (www.usp.org).

Stability test : -

Specimens for long term stability tests should be subject to dissolution testing and comply with the standards of the specifications.

- Stability requirements have been well established in national and international guidelines. In view of the urgency of availability of FDC products, it may be possible to consider limited stability data at the time of filing recognizing that the required stability data package will be provided at a later date.
- Stability studies should be designed with the geographic climate of the target market in mind.
- Repackaging of bulk finished product will require stability studies in the bulk container and the final container closure system. Expiration dating is linked to the manufacturing date of the dosage form.
- Methods that measure and indicate product stability should be developed.
- Instructions concerning storage conditions should be labeled and clearly visible.
- Alternative accelerated stability studies may be considered on a case by case basis and must be accompanied with a sound scientific justification.

Packaging : -

Packaging should be selected to ensure the quality of the final product throughout its shelf life. Repackaging of FDCs is discouraged. However, if repackaging is necessary, it should be in line with GMP principles as well as subject to appropriate release and control testing.

Inspections to assure compliance with GMPs and manufacturing of FDCs must be done according to internationally recognised GMPs acceptable to the regulatory authority (www.globalhealth.gov).

Formulation

Formulation of film coated ranitidine hydrochloride pellet compressed tablet:-

Product Information		
Ingredients Name	**Type**	**Strength**
Ranitidine Hydrochloride	Active	30mg in one tablet.
Excipients Name		**Types of Excipients**
Croscarmellose sodium	Inactive	Disintegrants
Hypromellose	Inactive	Binder and tablet coating material.
Magnesium stearate	Inactive	Lubricants and Glidants
Microcrystalline cellulose	Inactive	Fillers and Cushioning agent
Hydroxypropylmethyl cellulose	Inactive	Enteric film coating material
Triacetin	Inactive	Hydrophilic plasticizer
Titanium dioxide	Inactive	Coloring agent, Opacifying agent and Pigments
D&C Yellow No. 10 Lake	Inactive	Coloring agents and Pigments
Product Characteristics		
Route of Administration :- Oral		
Coating :- True		
Shape :- Spherical		

Formulation of enteric coated diclofenac sodium (diclofenac) pellet compressed tablet (http://dailymed.nlm.nih.gov):-

Product Information		
Ingredients Name	**Type**	**Strength**
Diclofenac sodium (diclofenac)	Active	75 mg in one tablet.
Excipients Name		**Types of Excipients**
Hydroxypropyl methyl cellulose	Inactive	Enteric film coating material, matrix binder and cushioning excipient.
Iron oxide	Inactive	Tablet Coating
Lactose	Inactive	Diluents or fillers
Magnesium stearate	Inactive	Lubricants and Glidants
Methacrylic acid copolymer	Inactive	Enteric film coating material.
Microcrystalline cellulose	Inactive	Binding agent and Cushioning agent
Polyethylene glycol	Inactive	Binder
Povidone	Inactive	Binder
Propylene glycol	Inactive	Tablet Coating
Sodium hydroxide	Inactive	Buffering agent
Sodium starch glycolate	Inactive	Disintegrant
Talc	Inactive	Lubricants and glidants
Titanium dioxide	Inactive	Colouring agent, Opacifying agent and Pigments
Product Characteristics		
Route of Administration :- Oral		
Coating :- True		
Shape :-Spherical		

Results and Discussions

It is possible to combine diclofenac and ranitidine together as enteric coated pellet compressed tablet form.

The literature contains many reports and experiments that has been done or studied on the combination preparation of diclofenac and ranitidine together in a single formulation which includes the efficacy, bioavailability and release profile of diclofenac-ranitidine combination in a single formulation and also the feasibility of formulating ranitidine and diclofenac into pellets.

If this formulation is prepared it can be effectively use in the therapy of NSAID-Induced Gastrointestinal disorders.

Discussions on the Formulations:-

►**The active ingredients**:- The active ingredients used in the present invention is diclofenac sodium ranitidine hydrochloride.

►**Binder:** Binder is selected from the group of cellulose derivatives such as hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), ethyl cellulose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, microcrystalline cellulose; polymethacrylates, sugars such as lactose, sucrose etc.; polyvinylpyrrolidone (PVP), waxes, fatty alcohols such as stearyl alcohol, cetyl alcohol; gelatin, starch, pregelatinized starch, carbomer; gums like xanthan gum, guar gum, acacia, alginates and mixtures thereof. Polymethacrylates such as Eudragit RL30D, Eudragit RLPO, Eudragit RL, Eudragit RS30D, Eudragit RSPO, Eudragit RS, Eudragit NE30D, Eudragit NE40D, Eudragit NM30D and Eudragit E are used. The binder is preferably selected from HPMC, HPC, PVP, microcrystalline cellulose, lactose and mixtures thereof.

Binder present in the core is up to about 40% by weight of enteric coated pellets, preferably from about 0.01% to about 20% by weight of enteric coated pellets, more preferably from about 0.1% to about 10% by weight and most preferably from 0.5% to about 5% by weight of enteric coated pellets.

For Ranitidine Pellet:- Hypromellose is used. Range-2-5% or 10-80% for high viscosity grades.

For Diclofenac Pellet: - Microcrystalline cellulose. Range-20-90%
Polyethylene glycol. Range-5%
Povidone. Range-0.5-5%

►**Fillers**:- Fillers are selected from the group of carbohydrates such as glucose, lactose, mannitol, sucrose, dextrose, sorbitol, fructose, sorbitol, compressible sugar, etc; calcium phosphate, dibasic calcium phosphate, tribasic calcium phosphate, starch, pregelatinized starch, starch 1500, cyclodextrins and its derivatives; carboxymethylcellulose and its salts such as sodium, potassium and calcium salt; calcium sulfate, microcrystalline cellulose, cetyl alcohol, stearyl alcohol, waxes and mixtures thereof.

For Ranitidine Pellet: - Microcrystalline cellulose. Range-20-90%

For Diclofenac Pellet: - Lactose. Range-10–50%

►**Surfactants**:- Surfactants are selected from the group of cationic surfactant, non-ionic surfactant and anionic surfactant and is preferably selected from sodium lauryl sulfate, polysorbates, sorbitan esters, poloxamers, fatty acid esters and ethers of polyethylene glycol, alkyl phenoxy polyethylene glycols, block polymers of polyethylene and polypropylene oxides, oleic acid and its salt, bile salts and their conjugates, octoxynol, polyoxyethylene and its derivatives such as castor oil derivatives polyoxyethylene monoalkyl ethers, sucrose esters, lanolin esters and ethers, lauric acid and its salts, alkyl sulfate and its salts, fatty acid and its salts and mixtures thereof.

►**Anti-adherents**: -Anti-adherents are selected from talc, colloidal silicon dioxide, magnesium stearate, calcium stearate, glyceryl monostearate, glyceryl behenate, sodium lauryl sulfate, stearic acid and mixtures thereof.

For Ranitidine Pellet: - Magnesium stearate. Range-0.25-5 %

For Diclofenac Pellet: - Magnesium stearate- Range-0.25-5 %

Talc. Range-1.0-10%

►**Buffers**: -Buffers and alkaline substances may be used singly or in mixtures and are selected from the group of alkali and alkaline earth metals hydroxides, carbonate, bicarbonate, sulphate, phosphates and oxides; and amino acids. It is preferably selected from one or more of oxides, hydroxides, carbonates, bicarbonates, phosphates and sulphates of sodium, potassium, calcium, zinc, magnesium and aluminium; the composite aluminium/magnesium compounds $Al_2O_3.6MgO.CO_2.12H_2O$ or $MgO.Al_2O_3.2SiO_2.nH_2O$, where n is not an integer but less than 2.

Buffers such as acetate, phosphate, borate, bicarbonate, carbonate, succinate, tris buffer, organic acid buffer and mixtures thereof may also be used. Preferably alkaline substance from monobasic sodium phosphate, dibasic sodium phosphate, tribasic sodium phosphate, sodium hydroxide, potassium hydroxide, sodium lauryl sulphate, magnesium carbonate, calcium carbonate, magnesium oxide and mixtures thereof are used.

For Diclofenac Pellet: -Sodium hydroxide. Range-8.6 - 10.6%

►**Disintegrating agent**:- Disintegrating agent is selected from the group of sodium starch glycolate, crospovidone, cross linked carboxymethylcellulose and its salts such as sodium, potassium and calcium salt; starch, modified starch, pregelatinized starch, starch 1500, microcrystalline cellulose and mixtures thereof.

For Ranitidine Pellet: -Croscarmellose sodium. Range-0.5-5 %

For Diclofenac Pellet: - Sodium starch glycolate. Range-2.0-8%

►**Pigments and colours**: - Pigments and colours are selected from pharmaceutically acceptable pigments and colours. Titanium oxide, iron oxide colours such as iron oxide red; lake colours such as lake of sunset yellow and mixtures thereof are preferably used.

For Ranitidine Pellet: - Titanium dioxide and D&C Yellow No. 10 Lake

For Diclofenac Pellet: -Titanium dioxide

►**Solvent:** -The solvent is selected from aqueous, alcoholic, hydro-alcoholic and organic solvents and is preferably selected from water, methanol, ethanol, isopropanol, acetone, dichloromethane and mixtures thereof. The solvent of choice for the preparation of the core is water.

Enteric Coat: -

The cores or separating layer coated cores of the present invention are coated with at least two enteric layers comprising of enteric polymers and plasticizer such that the last enteric layer is formed from a solution comprising of enteric polymer and plasticizer in organic solvent(s).

►**Enteric polymer**: -Enteric polymer in the enteric layers is selected from methacrylic acid copolymers, cellulosic polymers, polyvinyl alcohol phthalate, polyvinyl acetate phthalate, shellac and mixtures hereof. Methacrylic acid copolymers is selected from Eudragit L30D55 (Type C), Eudragit L10055 (Type C), Eudragit L100 (Type A), Eudragit L12.5, (Type A), Eudragit S100 (Type B), Eudragit S12.5 (TypeB) and Eudragit FS30D.
Cellulosic polymer is selected from cellulose acetate phthalate (CAP), cellulose acetate trimelliate (CAT), hydroxypropylmethylcellulose phthalate (HPMCP), cellulose propionate phthalate, hydroxypropylmethylcellulose acetate succinate (HPMCAS), cellulose acetate maleate and hydroxypropylmethylcellulose hexahydrophthalate.

The total enteric polymers are at least 20%, preferably 30% to 70%, more preferably 40% to 60% by weight of the enteric coated pellets.

The enteric coated pellets comprises of two or more enteric layers which differ in composition and ratio. In one aspect of the invention, the enteric coated pellets have two enteric layers; the ratio of enteric polymer in these two layers is 0.8:0.2 to 0.2:0.8. Enteric polymer or polymers is preferred in the range of 0.7: to 0.3 to 0.3:0.7, more preferably

from 0.6:0.4 to 0.4:0.6. In another aspect of the invention, the enteric coated pellets have three or more enteric layers; the enteric polymer(s) in one layer is at least 10% by weight of the total enteric polymers.

The enteric polymer which has been proposed in the study is a hydroxpropylmethylcellulose phtalate (HPMCP) which is conventionally used for providing enteric coating on solid dosage forms. It is, however, necessary that the HPMCP used in the present invention should have an average particle diameter of not exceeding 100 μm. This is because a HPMCP of coarser particles than 100 μm cannot give a stable dispersion in the aqueous dispersion medium. In addition, an aqueous dispersion containing such large particles of HPMCP may cause jamming of the nozzle of a spray gun used in the coating procedure and the coating film formed on the solid dosage form is sometimes inferior in smoothness due to the presence of coarser particles.

For Ranitidine Pellet: - Hydroxypropylmethyl cellulose

For Diclofenac Pellet: -Hydroxypropyl methylcellulose, methacrylic acid copolymer and iron oxide.

► **The organic solvent**:-The organic solvent used is selected from methanol, ethanol, isopropanol, acetone, dichloromethane and mixtures thereof.

► **Plasticizer**:-Plasticizer is selected from the group of hydrophilic and/or hydrophobic plasticizers and is selected from polyethylene glycol, triacetin, triethylcitrate, acetyl triethylcitrate, miglyol, cetyl alcohol, acetyltributylcitrate, diethyl phthalate, dibutyl phthalate, propylene glycol, hydrogenated oils, dibutylsebacate, meglumine and mixtures thereof and is preferably dibutyl sebacate. Plasticizers in the enteric layers is up to 15%, preferably up to 12.5%, more preferably up to 10% by weight of enteric polymer.

For Ranitidine Pellet: - Triacetin. Range-10-35%

Challenges of this Combined Dosage Form

If this formulation is formed then there are some precautions that must be taken while using this medicine.

Patient must remember that certain medicines, such as aspirin, and certain foods and drinks (e.g., citrus products, carbonated drinks) irritate the stomach and may make your problem worse.

Cigarette smoking tends to decrease the effect of H2-blockers diclofenac by increasing the amount of acid produced by the stomach. This is more likely to affect the stomach's nighttime production of acid. While taking H2-blockers, smoking should be completely stopped.

Drinking alcoholic beverages while taking an H2-receptor antagonist and diclofenac has been reported to increase the blood levels of alcohol. So patient should consult their health care professional for guidance.

Along with its needed effects, a medicine may cause some unwanted effects. Although not all of these side effects may occur, if they do occur they may need medical attention.

Patient should visit their doctor as soon as possible if any of the following side effects occur: -

For Ranitidine bleeding or crusting sores on lips, blistering, burning, redness, scaling, or tenderness of skin, blisters on palms of hands and soles of feet, changes in vision or blurred vision, confusion, coughing or difficulty in swallowing, dark-colored urine, dizziness, fainting fast, pounding, or irregular heartbeat, fever and/or chills, flu-like symptoms, mood or mental changes, including anxiety, agitation, confusion, hallucinations (seeing, hearing, or feeling things that are not there), mental depression, nervousness, or severe mental illness, muscle cramps or aches, nausea, vomiting, or loss of appetite, pain, shortness of breath, skin rash or itching, sore throat, constipation etc.

Most important fact about diclofenac is patient should be under frequent checkups. This medication should not be used if patient have certain medical conditions. Before using this medicine, patient should consult a doctor or pharmacist if they have: aspirin-sensitive asthma (a history of worsening breathing with runny/stuffy nose after taking aspirin or other NSAIDs), recent heart bypass surgery certain liver problem (hepatic porphyria), medical history, especially of: kidney disease, liver disease, poorly controlled diabetes, asthma, growths in the nose (nasal polyps), stomach/intestine/esophagus problems (e.g., bleeding, ulcers), heart disease (e.g., congestive heart failure, history of heart attack), high blood pressure, stroke, swelling (edema, fluid retention), a severe loss of body water (dehydration), blood disorders (e.g., anemia), bleeding or clotting problems. This drug may make you dizzy or drowsy; use caution while engaging in activities requiring alertness such as driving or using machinery.

The elderly may be more sensitive to the side effects of this drug, especially stomach/intestinal bleeding and kidney effects. This medication should be used only when clearly needed during the first 6 months of pregnancy. It is not recommended for use during the last 3 months of pregnancy due to possible harm to the unborn baby and interference with normal labor/delivery. Discuss the risks and benefits with your doctor. This drug passes into breast milk. While there have been no reports of harm to nursing infants, consult your doctor before breast-feeding.

Limitations

The major limitation of this study is that it has been proposed theoretically. No practical work has been done due to shortage of laboratory support and unavailability of different kind of excipients. To perform this study various type of equipments are required such as for the manufacture of pellets, powder layering technique requires specialized equipment such as a rotary-tangential fluidized bed or modified rotating pans. For the application of enteric layer to the pellets fluidized bed coater is required. All these equipments are not available in our University laboratory. And to perform this study industrial atmosphere is required without industrial facilities this formulation cannot be made effectively.

Conclusion

This study has been proposed theoretically only. So practical work/experiment need to be done. More studies are needed to assess its efficacy in different patient, populations, its cost-effectiveness and, in particular, its long-term safety.

Compression of coated pellets is a challenging task necessitating the optimization of various formulation and process variables. Certain formulation and process parameters play an important role in successful production and functioning of the multiple unit-containing tablets. This article reviews those key formulation variables.

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