Drugs Using Natural Super Disintegrants

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Abstract

Recent advances in novel drug delivery system aims to enhance safety and efficacy by the formulating a convenient dosage form for administration to achieve the better patient compliance. One of the approaches is formulation of rapidly disintegrating tablets. These are useful for pediatric, geriatric and also dysphagic patients, leading to improved patient compliance. These dosage forms dissolve or disintegrate rapidly in the oral cavity within a matter of seconds without the need of water. Combination of solid dispersion and natural super disintegrants is a promising approach to prepare efficient rapidly disintegrating tablets of poor water-soluble drugs.

INTRODUCTION

In the all the dosage forms taken orally, the tablet is one of the most used dosage forms. Disintegrants are substances integrated to tablet and some encapsulated formulations to enhance the breakup of the tablet and capsule "slugs" into more small particles in an aqueous environment thereby increasing the available effective surface area and increasing a more rapid release of the substance. The faster the drug goes into solution, quicker the absorption and onset of clinical effect. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablets dosage form. The importance of these dosage forms are increasingly being recognized in both, industry and academics also. Patients who may have difficulty swallowing tablets or liquids, traditional tablets and capsules administered with one glass of water may be inconvenient or impractical for some patients. However, some patients, particularly pediatric and geriatric patients, have difficulty swallowing or chewing solid dosage forms. Many pediatric and geriatric patients are unwilling to take these solid preparations due to fear of choking. For example, a very elderly patient may not be able to swallow a daily dose of antidepressant in the form of a Caplet shaped Tablet. Recent trends in pharmaceutical formulation development technology have presented viable dosage alternatives for example; an eight-year-old with allergies could use a more convenient dosage form than antihistamine syrup. A schizophrenic patient in the institutional.

Literature Review

Vishal Dhiman *et al.*, 2013 Telmisartan is an Anti-hypertensive drugs which is insoluble in water, hence the drug may be slowly or incompletely dissolves in the gastro-intestinal tract. So the rate of dissolution and therefore its bioavailability is less(bioavailability 42%). In the present study an attempt has been made to prepare Fast Dissolving tablets of Telmisartan by using Superdisintegrants– Cross carmellose sodium, Microcrystalline cellulose and sodium starch glycolate, level of addition to increase the rate of drug release from dosage form to increase the dissolution rate and hence its bioavailability. The tablets were prepared by Direct Compression methods and the prepared blend and tablets were evaluated for their physicochemical properties and In-Vitro dissolution study. The evaluation studies were performed suchas Weight Variation, Thickness, Hardness, Disintegrating Time, Wetting Time, and In-Vitro Drug Release. The Disintegration time of Fast Dissolving tablets were increased by the addition of concentration of Superdisintegrants.

Anasuya Patil *et al.*, 2016 The objective of this study was formulation, development and evaluation of Diltiazem hydrochloride fast dissolving tablets. FDTs were prepared by various methods including direct compression method where various superdisintegrants like Crospovidone, Croscarmellose sodium and Sodium starch glycolate in concentration range of 2-6%w/w. Diltiazem hydrochloride FDTs were also prepared by sublimation technique where different subliming agents (5%w/w) camphor, ammonium bicarbonate were used with 6%w/w Sodium starch glycolate asa superdisintegrant. Prepared tablets later exposed to vacuum. The prepared FDTs from two methods were evaluated for weight variation, thickness, drug content, friability, hardness, wetting time, in vitro disintegration time and in-vitro dissolution study. All prepared formulations were showed disintegration time ranging from 25 to 120 sec. All the

prepared formulae complied with the pharmacopoeial requirements ofthe drug contents. F10 prepared formulations gave the less in-vitro disintegration (25.32±0.258sec) and increased percentage cumulative released of 78.11±0.16 after 10min. In conclusion the results of this work suggest that fast dissolving tablets of Diltiazem hydrochloride with rapid disintegration time, fast drug release and good hardness can be efficiently and successfully formulated by employing sublimation methods.

From the above literature, I understood the need of the improvement of bioavailabilityof poorly soluble drugs by development of solid dispersions. Various authors developed solid dispersions and fast dissolving tablets of various drugs using synthetic super disintegrants. It increases the cost of the manufacturing and may not be affordable by all the patients. So, an attempt was made to development of rapidly disintegrating tablets of selected drugs with improved bioavailability and decreased cost. In this present study selected natural super disintegrants are readily available andcost effective.

Drugs to be promising incorporate in RDTS

There are no particular limitations as long as it is a substance which is used as a pharmaceutical active ingredient.

Analgesics and Anti-inflammatory Agents:

Aloxiprin, Auranofin, Azapropazone, Benorylate, Diflunisal, Etodolac, Fenbufen, Fenoprofen Calcium, Flurbiprofen, Ibuprofen, Indomethacin, Ketoprofen,Meclofenamic Acid, Mefenamic Acid, Nabumetone, Naproxen, Oxaprozin, Oxyphenbutazone, Phenylbutazone, Piroxicam, Sulindac.

STRATEGIES FOR THE IMPROVEMENT OF BIOAVAILABILITY OF THE DRUGS

Hence, two areas of pharmaceutical research that focus on improving the oral bioavailability of active agents include (i) enhancing solubility and dissolution rate of poorly water-soluble drugs and (ii) enhancing permeability of poorly permeable drugs

Drug release is a crucial and limiting step for drug bioavailability particularly for drugs with low gastrointestinal solubility and high permeability. By improving the drug release profile of these drugs, it is possible to enhance their bioavailability and reduce side effects.

Class I: The drugs of this class exhibit high absorption and high dissolution. The bioavailability will depend solely on the gastric emptying rate. These compounds are well absorbed and their absorption rate is usually higher than the excretion rate. Examples include metoprolol, diltiazem, verapamil, and propranolol.

Class II: The drugs of this class have high absorption but low dissolution. In vivo drug dissolution is the rate-limiting step for absorption. A small increment in dissolution may result in drastic improvement in the bioavailability. Hence, the enhancement of dissolution is the key factor in formulating BCS class II drugs. The bioavailability of these products is limited by their solvation rates. Examples include glibenclamide, phenytoin, danazol, mefenamic acid, nifedipine, ketoprofen, naproxen,carbamazepine and ketoconazole.

Class III: The drugs of this class have high dissolution but low absorption. Drug permeability is the rate-limiting step for drug absorption, but the drug is dissolved rapidly. These drugs exhibit a high variation in the rate and extent of drug absorption. Since the dissolution is rapid, the variation is attributable to alteration of physiology and membrane permeability rather than the dosage form factors. Examples include cimetidine, ranitidine, acyclovir, neomycin B, atenolol, and captopril.

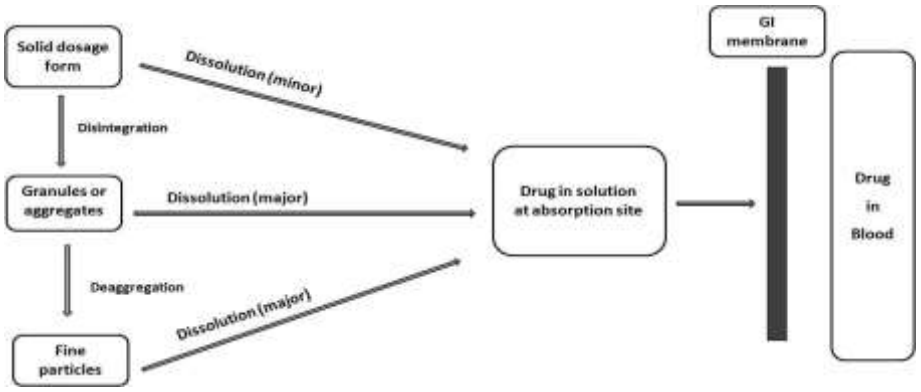
Class IV: The drugs of this class are problematic for effective oral administration. BCS class IV drugs exhibit challenging molecular properties such as low solubility and low permeability. These compounds have poor bioavailability. They are usually not well absorbed through the intestinal mucosa. Since both solubility and permeability are rate-limiting steps for absorption, it would be considered that physiological factors, for example, gastric emptying time and gastrointestinal transit time, highly influence the absorption of BCS class IV drugs. These drugs exhibit largeinter and intra subject variation in terms of absorption resulting difficulty in formulation development. Examples include hydrochlorothiazide, taxol, and furosemide.

The solubility problems of BCS class II drugs and methods for overcoming the solubility limitations are to be identified and applied commercially so that potential therapeutic benefits

of these active ingredients can be realized. The increase in the amount of drug dissolved at the absorption site usually results in improvement in bioavailability. Two strategies are employed to achieve this; i) Improvement insolubility and ii) Enhancement in dissolution rate.

Schematic representation of the dissolution process of a olid osage form

Over the years, a number of different strategies have been developed in order to overcome these limitations. Some of these efforts include salts formation, use of surface-active agents,



prodrugs, particle size reduction (Micronization), co-solvency, hydrotropic solubilization, cyclodextrin complexation, wettability, micellar solubilization, pH modification and screening for more soluble analogues.

However, there are some practical limitations to the few of above mentioned techniques as mentioned in Table 1.1. Hence, the need of novel strategies has been thedriving force for the development of technologies to improve the bioavailabilityrelated problems of poorly water-soluble drugs.

Drugs in amorphous state: Poor water soluble crystalline drugs, when in the amorphous state tend to have higher solubility. The enhancement of drug release can usually be achieved using the drug in its amorphous state, because no energy is required to break up the crystal lattice during the dissolution process. In solid dispersions, drugs are presented as supersaturated solutions after system dissolution; aunit is speculated that, if drugs precipitate, it is as a meta-stable polymorphic form with higher solubility than the most stable crystal form. For drugs with low crystal energy (low melting temperature or heat of fusion), the amorphous composition is primarily dictated by the difference in melting temperature between drug and carrier. For drugs with high crystal energy, higher amorphous compositions can be obtained by choosing carriers, which exhibit specific interactions with them.

Preparation of solid dispersions by Fusion (Melt) Method

Solid dispersions of drugs with different carriers (PEG 6000, PEG 20000 and Gelucire 50/13 in different weight ratios were prepared by the fusion (Melt) method. Accurately weighed amounts of carriers were placed in a china dish, kept on hot plate and melted with continuous stirring, at a temperature of about 50-60°C. An accurately weighed amount of drug was incorporated into the molten carrier(s) with stirring to ensure homogeneity. The mixture was heated until a clear homogeneous melt was obtained. The china dish was then removed from the hot plate and melt was transferred onto an aluminum pan, allowed to cool at room temperature. The dried solid dispersions were pulverized and sieved through sieve number 60#. The samples were stored in amber colored bottles capped with rubber corks and kept in desiccators

PHARMACOKINETIC STUDIES OF THE OPTIMIZED TABLETS IN RABBITS

The objective of the *in vivo* studies in rabbits was to demonstrate the improvement of bioavailability of poorly soluble drugs by solid dispersion technology. The major goal to conduct the pharmacokinetic studies in rabbits was to describe the time course of drug concentrations in blood in mathematical expressions.

Exploration on the pharmacokinetics of drugs from their dosage forms is a significant and essential part of research studies and provides the key information related to bioavailability of the newly developed formulations. So the present study was aimed to conduct *in vivo* pharmacokinetic studies to prove the improvement in bioavailability of drug from the

optimized formulation.
This part of the study interprets in vivo pharmacokinetic investigations of KF11 solid dispersion of Ketoprofen to verify enhancement of dissolution and absorption rate when contrasted to pure drug. The objective of the in vivo pharmacokinetic investigations was to recount the time course of Ketoprofen concentrations in blood.
The AUC i.e., area under the curve is an important parameter for comparative bioavailability study and the others such as T_{max} and C_{max} are also key parameters thatrelated to therapeutic efficiency of drugs. MRT is able to explain the tendency of drugto remain in the body.

SUMMARY AND CONCLUSION

The research work in the present thesis describes solid dispersion approach for the enhancement of solubility, dissolution and oral bioavailability of poorly soluble drugs Flurbiprofen, Ketoprofen and Aceclofenac. And also the effect of natural superdisintegrants in the development of rapidly disintegrating tablets.
Initially, an introduction part briefly explains about solid dispersion, rapidly disintegrants tablets, benefits of natural super disintegrants after this the drug profile and excipients profile are described which are used in the study. Extensive literature survey was done for the collection of theoretical and technical data. The experimental part includes the explanation of implemented methods in the present study.
All the drugs are non-steroidal anti-inflammatory drugs (NSAIDS). These are non selective COX inhibitor and are one of the most effective NSAIDs to hinder the prostaglandin. All the three drugs are classified as BCS class II drugs due to their low aqueous solubility and high permeability. They have low oral bioavailability; it is due to their poor aqueous solubility and dissolution rate limited absorption. Hence, it is necessary to enhance the aqueous solubility and dissolution rate of Flurbiprofen, Ketoprofen and Aceclofenac to obtain faster onset of action, minimize the variability in absorption and improve their overall oral bioavailability.
The present study deals solid dispersion technology using different carriers like PEG 6000, PEG 20,000 and Gelucire 50/13 to improve the dissolution and/or solubility andthere by bioavailability of poorly soluble drugs. Solid dispersions were prepared by solvent evaporation method.
The natural superdisintegrants involve various natural substances like gums,mucilages, and other substances of natural origin which are more effective at lower concentrations with greater disintegrating efficiency, mechanical strength, more economical and easily availability.
Combination of solid dispersion and natural super disintegrants is a promising approach to prepare efficient rapidly disintegrating tablets of poor water soluble drugs these are Flurbiprofen, Ketoprofen and Aceclofenac. Rapidly disintegrating tablets delivery Systems are easy to administer and handle hence, leads to better patient compliance. Usually, elderly people experience difficulty in swallowing the conventional dosage forms (tablets, capsules, solutions and suspensions) because of tremors of extremities. In the oral cavity drug then enters the stomach as finer particles, which may get rapidly dissolved in the gastric fluid due to the larger surface area of the drug particles which increases bioavailability leading to faster onset of action.

FUTURE SCOPE OF THE STUDY

Design and develop the Rapidly Disintegrating tablets to improve bioavailability of the poorly soluble drugs. Improve solubility of drug where absorption is found to be more. Establish invitro and invivo correlation to guarantee the efficacy and bioavailability of Rapidly Disintegrating tablets. Find the feasibility of the action of the proposed Rapidly Disintegrating tablets under invivo conditions. The basic approach in the study was development of rapidly disintegrating tablet is provide instantaneous disintegration of tablet after putting on tongue, their by release the drug in saliva. The bioavailability of some drugs may be increased due to absorption of drug in oral cavity and also due to pregastric absorption of saliva containing dispersed drugs that pass down into the stomach. More ever, the amount ofdrug that is subjected to first pass metabolism is reduced as compared to standard tablet.

LIMITATIONS OF RESEARCH WORK

- The tablets usually have insufficient mechanical strength. Hence, careful handling is

required.

- The tablets may leave unpleasant taste and/or grittiness in mouth if not formulated properly.
- Drugs with relatively larger doses are difficult to formulate into RDT e.g. antibiotics like amoxicillin with adult dose tablet containing about 500 mg of the drug.
- Patients who concurrently take anticholinergic medications may not be the best candidates for RDT.
- Similarly patients with dryness of the mouth due to decreased saliva production may not be good candidates for these tablet formulations.

From different studies conducted on peels, it has been found that peels of fruits and vegetables hold a tremendous potential to serve as a source of newer, effective, safer and better antioxidant and antimicrobial agents.

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