ENHANCEMENT OF SOLUBILITY AND DISSOLUTION OF A DRUG MEFENAMIC ACID

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ABSTRACT

Mefenamic acid is a poorly water-soluble drug (BCS Class II), widely prescribed for mild to moderate pain, primary dysmenorrheal, rheumatoid arthritis, osteoarthritis and other joint diseases.Inorder to increase its solubility and dissolution rate, various solubility enhancement methods like solvent evaporation, trituration, ball milling, physical mixing andnon-solvent methods in chitosan carrier, with different mefenamic acid to chitosan ratios have been investigated. Drug-carrier interactions were investigated by differential scanning calorimetry and FT-IR spectroscopy. The studies showed that solubility and dissolution rate of mefenamic acid were distinctively increased in the prepared binary mixture compared to that of pure mefenamic acid. The increase of dissolution rate was related to the ratio of mefenacmic acid to chitosan and the method employed.Cogrinding methods (Trituration and ball milling) were the most effective techniques, showing the strongest amorphizing effect of chitosan. The drug-carrier binary mixtures (Mefenamic acid- chitosan = 1:10 w/w)gave the highest dissolution rate, i.e., about 19.2-fold higher than that of the pure mefenamic acid.

Keywords: Mefenamic acid; Chitosan; Dissolution enhancement; Ball milling; Amorphization.

INTRODUCTION

Drugsolubility:

Oral formulation has been the preferred and most common route of drug delivery around the globe. The popularity of this dosage form is owing to its ease of administration and good patient compliance. From drug development and formulation perspective, a solid dosage form offers superior stability compared to intravenous formulations. Therefore, most of the new chemical entities (NCE) under development these days are intended to be used in a solid dosage form that originate an effective and reproducible in vivo plasma concentration after oral administration.

But for many drugs, formulation of solid dosage form can be an inefficient mode for administration as approximately 40% or more of the NCE being generated through drug discovery programs have problem in water-solubility [1]. For drugs with poor aqueous solubility,dissolution is the rate limiting step forits bioavailability.

The therapeutic effect of drugs depends on the drug concentration at the site of action. The absorption of the drug into the systemic circulation is a pre requisite to reach the site of action for all drugs, except those drugs that are applied at the site of action, or intravenously injected. After oral administration many factors determine the bioavailability.Since only dissolved drug can pass the gastro intestinal membrane, dissolution is one of those factors. However, drug metabolism in the intestinal lumen, the intestinal wall and the liver may also reduce its bioavailability .In general it can be stated that the rate of absorption, therefore, onset and extent of the clinical effect, is determined by the dissolution of the drug and the subsequent transport through the biological

membrane.Therefore,together with the permeability, the solubility and dissolution property of a drug are key determinants of its oral bioavailability.

Solubility is one of the key parameter in Biopharmaceutical Classification System(BCS), and dissolution rate is the most essential factor controlling the bioavailability of drugs. A compound with solubility of less than 1 part per 10,000 part of water is categorized as poorly water soluble drug [2]. A poorly water soluble drug, more recently, has been defined in general terms as the one which requires more time to dissolve in the gastrointestinal fluid than it takes to be absorbed in the gastrointestinal tract.

Solid dispersions:

Chiou and Riegelman [8] defined the term solid dispersion as 'the dispersion of one or more active ingredients in an inert carrier matrix at solid-state prepared by the melting(fusion), solvent or melting- solvent method'. On the other hand, Corrigan [9] suggested the definition as 'product formed by converting a fluid drug-carrier combination to the solid state'.

Several insoluble drugs have been shown to improve the dissolution character when incorporated into solid dispersion and has been widely employed to improve the dissolution rate and solubility of poorly water soluble drugs [10,11]. Solid dispersions release the drug through different mechanisms, and the rate of release of drug to the surrounding fluid is mainly dependent on the type of solid dispersion formed [12,13].

Preparation techniques of solid dispersions:

Solvent evaporation method: In this method, physical mixtures of two components are dissolved in a common solvent and the solvent is removed by evaporation. The advantage soft his method are low temperature requirement for the preparation of dispersion and thermal decomposition of drugs v and carriers v can be prevented.The higher cost of production, incomplete removal of solvent ,adverse effects of solvent on the chemical stability of the drug and selection of common solvent are the drawbacks of this method.

Melting method (Fusion method)

The physical mixture of drug and water- soluble carrier was heated to melt and the molten mixture is then cooled and solidified mass was pulverized. The melting point of a binary system depends on its composition and proper manipulation of drug-carrier ratios. The method is limited by the thermal decomposition of drug-carrier system,which can be avoided by controlling fusion time and rate of cooling.

Kneading method

The physical mixture of drug and carrier is triturated using small quantity of organic solvent and water mixture, usually alcohol and water. The slurry is kneaded and dried in hot air oven and pulverized. The advantages of this method are low temperature requirement for solid dispersion preparation and usage of organic solvent is less.This method of preparation avoids thermal degradation of drug and employs less quantity of organic solvents.

Melting solvent method

This method involves dissolving the drug in a suitable solvent and incorporation of the solution directly into the molten carrier. This method possesses the advantages of both solvent and melting methods.

Supercritical fluid methods

Supercritical fluid methods are mostly applied with carbondioxide(CO_2),which is used as either a solvent for drug and matrix or as an antisolvent.This technique consists of dissolving the drug and the carrier in a common solvent

that is introduced into a particle formation vessel through a nozzle, simultaneously with CO2.When the solution is sprayed, the solvent is rapidly extracted by the SCF, resulting in the precipitation of solid dispersion particles on the walls and bottom of the vessel . This technique does not require the use of organic solvent and since CO2 is considered environmentally friendly, this technique is referred to as 'solvent free'. This technique is known as Rapid Expansion of Supercritical Solution (RESS).

The advantages of solid dispersions:[15]

Management of the drug release profile using solid dispersions is achieved by manipulation of the carrier and solid dispersion particles properties. Parameters such as carrier molecular weight and composition, drug crystallinity ,and particle porosity and wettability ,when successfully controlled, can produce improvements in bioavailability.

SUMMARY

Oral formulation has been the preferred and most common route of drug delivery around the globe . The popularity of this dosage form is owing to its ease of administration and good patient compliance .However,for many drugs, formulation of solid dosage form can beaninefficient mode for administration as approximately 40%or more of the NCE being generated through drug discovery programs have problem in water-solubility.For drugs with poor aqueous solubility ,dissolution is the rate limiting step for its bioavailability.

Mefenamic acid a non-steroidal anti-inflammatory drug (NSAIDS) was selected asthe model drug and belongs to BCS class-II having low solubility and high membrane permeability.

By preparing binary mixtures by various method sand with varied chitosan composition, a significant improvement in solubility and dissolution was observed. All the binary mixtures have shown a uniform drug content, and increment in the solubility and in vitro drug dissolution rate in distilled water compared to drug alone.

The evaluation parameters were carried out, from the FTIR analysis reports, it was confirmed that there was no any chemical modification and hence drug-carrier interaction was not observed. Whereas, from the DSC results, a considerable reduction in crystillinity of MA was observed in the prepared binary mixtures.

The method of binary mixture prepared had a marked influence on the solubility enhancement.Binary mixture prepared by ball milling and trituration showed a higher solubility in comparison to other methods.

The dissolution and solubility parameters progressively improved with increasing the polymer proportion in the binary mixtures and reached the highest value satthe1:10(w/w) drug-polymer ratio.Comparatively,co-grinding methods (trituration and ball milling methods) have shown a significant improvement in solubility and dissolution profile than other binary mixtures. A considerable wetting effect of chitosan was also observed on the binary mixtures, which assisted in enhancement of the solubility and drug dissolution rate. The stability studies of binary mixtures have shown a good stability throughout the stability studies at 40º Cand RH75%, in terms of drug content and in vitro dissolution.

Molecular dispersions as solid dispersions represent the last state on particle size reduction, and after carrier dissolution the drug is molecularly dispersed in the dissolution medium. Solid dispersions apply this principle to drug release by creating a mixture of a poorly water soluble drug and highly soluble carriers.A high surface are ais formed,resulting in an increased dissolution rate and consequently, improved bioavailability.

Particles with improved wettability:

Strong contribution to the enhancement of drug solubility is related to the drug wettablity improvement in solid dispersions. It was observed that even carriers without any surface activity, such as urea improved drug wettability and carriers with surface activity,such as cholic acid and bile salts, when used, can significantly increase the

wettability properties of drugs. Moreover, carriers can influence the drug dissolution profile by direct dissolution or co-solvent effects.

Particles with higher porosity

Particles in solid dispersions have been found to have a higher degree of porosity.The increase in porosity also depends on the carrier properties,for instance,solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymer sand ,therefore, result in a higher dissolution rate.The increased porosity of solid dispersion particles also hastens the drug release profile.

Drugs in amorphous state:

Poorly water soluble crystalline drugs, when in the amorphous state tend to havehigher solubility. The enhancement of drug release can usually be achieved using the drug inits amorphous state, because no energy is required to break up the crystal lattice during thedissolutionprocess.

Need for the study:

In the Biopharmaceutical classification system(BCS) ,drugs with low aqueous solubility and high membrane permeability are categorized as Class II drugs.Mefenamic acid(MA), a non-steroidal anti-inflammatory drug (NSAIDS) was selected as the model drug and belongs to BCS class-II having low solubility and high membrane permeability [16,17,18] .It is highly prescribed for mild to moderate pain,primary dysmenorrheal ,rheumatoid arthritis, osteoarthritis and other joint diseases. However, its bioavaibility is very low, probably due to poor water solubility (0.004%) [19] and insufficient dissolution rate.MA also acts as an irritant to the grastrointestinal mucosa when administered orally [20]. Thus there is a need to find an approach to increase its solubility and hence oral bioavailiability by enhancing its dissolution rate and also to reduce its grastric irritant effect by using suitable carriers like chitosan.

Chitosan is a naturally occurring structural polysaccharide that has recently emergedas most promising biopolymer for variety of potiential application in both biomedical and pharmaceutical fields .It is effective in enhancing the dissolution properties and bioavailability of poorly-soluble drugs. Further, its antacid and antiulcer properties can beutilized to prevent or reduce gastric irritation induced by MA [21].

Amorphous solid dispersions as a strategy to improve the bioavailability of poorly water-soluble compounds was employed [41]. In this study, the dissolution profiles of solid dispersions off elodipine formulated with poly (vinylpyrrolidone), hydroxy propyl methyl cellulose or hydroxy propyl methyl cellulose acetate succinate(HPMCAS)was compared. HPMCAS was found to maintain the highest level of super saturation for the greatest length of time for both the dissolution and solution crystallization experiments,where as PVP was found to be the least effective crystallization inhibitor. All polymers appeared to reduce the crystal growth rates of felodipine and thus enhanced the dissolution.

METHODOLOGY

Preparation of 0.1N HCl solution(pH1.2):

Simulated gastric fluid (0.1 N HCl, pH 1.2) was prepared by adding 50 ml of 0.2 M potassium chloride in a 200ml volumetric flask. Then 85 ml of 0.2 M HCl was transferred toit and the volume was made up with distilled water [42]. The buffer was prepared about 1 h prior to commencement of the experiments.

Preparation of phosphate buffer (pH7.4):

Phosphate buffer (pH7.4) prepared by the method described in Indian Pharmacopoeia [42]. 50 ml of 0.2 M potassium dihydrogen phosphate was transferred to a200 ml volumetric flask. After addition of 39.1 ml of 0.2 M sodium hydroxide, distilled water was added to make up volume and mixed thoroughly.

Development of calibration curve for mefenamic acid:

Mefenamic acid was weighed accurately (100 mg) using digital analytical balance and transferred to 100 ml volumetric flask, dissolved in 0.1 N NaOH solution and the final volume was made upto 100 ml with 0.1 N NaOH solution to get a stock solution A (1000µg/ml).

From the stock solution A, 10 ml was pipetted out into 100 ml volumetric flask and the final volume was made upto 100 ml with 0.1N NaOH solution, to get stock solution B(100 µg/ml). From the stock solution B, further serial dilutions were made with 0.1N NaOH solution to get the solutions in the range of 2-20 µg/ml concentration. The absorbance of the samples was recorded at 285 nm using UV-Visible spectrophotometer (UV-1601, Shimadzu,Japan)against 0.1 N NaOH solution as blank.

Preparation of drug-carrier binary mixtures

Before the preparation of the binary mixtures, drug and carrier were sieved throughsieve(# 80). Sieved samples were used for further studies.

Physical mixture method:

Required quantity of drug and chitosan was accurately weighed and taken in a clean,dry glass bottle (50 ml capacity). It was subjected to thorough mixing by keeping the bottle in tumbling mill. Tumbling mill was run for 30 minutes at a speed of 90 rpm/min. The prepared drug-carrier binary mixture were placed in an air tight container and stored in a desiccator until further use.

Trituration method:

Required quantity of drug and chitosan was accurately weighed and taken in a clean,dry glass porcelain mortar. Powder was thoroughly triturated with pestle for 30 minutes, and was passed through sieve no # 80. The prepared drug-carrier binary mixtures were packed in an air tight container and stored in a desiccator until further use.

Ball mil method:

Required quantity of drug and chitosan was accurately weighed and taken in a clean,dry ball mill with four steel balls of diameter 1 cm. The powder was subjected to thorough mixing by rotating the ball mill at optimum speed (90rpm/min) for 30 minutes .The prepared binary mixtures were packed in an airtight container and stored in a desiccator until further use.

Solvent evaporation method:

About 150 mg of drug was dissolved in 15 ml of acetone in a beaker. Required quantity of chitosan was added and triturated for 10 minutes. The paste was then transferred to a china dish and dried in hot air oven at 50˚ C for 1 h. The obtained powder was passed through sieve no # 80. The prepared binary mixtures were packed in an air tight container and stored in a desiccator until further use.

Non-solvent method:

To 0.5% w/v chitosan solution (40 ml), 100 mg drug solution in 10 ml acetone was added and stirred for 10 min. The mixture was poured into100 ml methanol and again stirred for 10 min. The final mixture was vacuum filtered and the residue was dried at 50º Cfor 1 h (N-I). Similarly, another set of the mixture was poured into 100 ml of

distilled water,filtered and dried(N-II).The product obtained was packed in an air tight container and stored in a desiccator until further use.

SUMMARY

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The stability studies of binary mixtures have shown a good stability through out the stability studies at 40º C and RH 75%, in terms of drug content and in vitro dissolution.

CONCLUSION

Looking into the future, more BCS class II drug are likely to be produced and the delivery of these molecules through the oral route is expected to be a continuing challenging.

Mefenamic acid, a BCS class II has very low bioavaibility, probably due to poor wate solubility (0.004%) and insuffient dissolution rate.

The various method like trituration, ball milling, physical mixing, solvent method and non-solvent method using hydrophilic carrier chitosan were employed to enhance solubility and dissolution rate. The evaluated parameters showed decrease in crystallinity of MA. The binary mixtures prepared by trituration method showed a most effective method showing a better solubility and dissolution rate compared to other methods. While chitosan had a profound positive effect, and with an increment in chitosan concentration it showed a propositionally increase in the solubility and dissolution rate.A simple trituration and ball milling methods (co-grinding), have lead to a significant improvement in solubility and dissolution profile, without using organic solvents and high temperature which appears to be the easier and most convenient method from a practical point of view.

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