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Research Article

Enhancement of Solubility of Diclofenac Sodium by Pastillation Method

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Abstract

The Diclofenac Sodium is BCS class II drug which comes under the antipyretic class drug, and has a wide range of use. But due to its low solubility it has low dissolution rate and hence reduced bioavailability. There are several methods for the enhancement of solubility and dissolution rate. Pastillation technique is widely employed in chemical industry for solidification and better handling. Pastilles are solidified discrete units, acquired directly from the melt mass. However, this method of pastillation has not been explored for the drug delivery system yet. Literature reveals that it can be used as a novel, effective and easiest method for the enhancement of solubility and dissolution rate. The selection of polymer was done by the solubility studies and Kolliphor HS 15 was used to make the pastilles of Diclofenac Sodium. Formation of pastilles were confirmed by FT-IR and further evaluated for % yield, drug contents, solubility study and dissolution test. From the results it was concluded that, solubility of Diclofenac Sodium was increased by pastillation method by 2-fold and dissolution rate was also enhanced by double than that of the drug. Thus, pastillation can be an effective and easiest method to enhance the solubility, dissolution rate and bioavailability of poorly water-soluble drugs having good permeability.

Keywords: Diclofenac Sodium, Pastillation, Kolliphor HS 15, Solubility enhancement, Solid dispersion.

INTRODUCTION

Oral administration is the most convenient and commonly employed route of drug delivery due to ease of administration, high patient compliance, cost effectiveness and flexibility of design of dosage form. Solubility is one of the important parameters to achieve desired concentration of drug in systemic circulation for achieving pharmacological response. Poorly water-soluble drug often requires high doses in order to reach therapeutic plasma concentration¹. The poor solubility and low dissolution rate in an aqueous gastrointestinal fluid often cause insufficient bioavailability. Especially for BCS class II drug substance like Diclofenac Sodium which is having poor aqueous solubility and poor oral bioavailability². The bioavailability can be enhanced by increasing the solubility and dissolution rate of the drug in gastrointestinal fluid. As for BCS class II drug rate limiting step is drug release from and solubility in the gastric fluid and not the absorption, so increasing the solubility in turn increase the bioavailability for BCS class II drugs³.

Pastillation is the process in which the solid dispersion using the drug and the polymer is made. Then this dispersion is placed in the glass syringe and then as the heat is applied by the heating coil then this hot molten mass is allowed to fall drop by drop on the metallic plate with cooling system. The over them the hot droplets solidify and form the pastilles⁴.

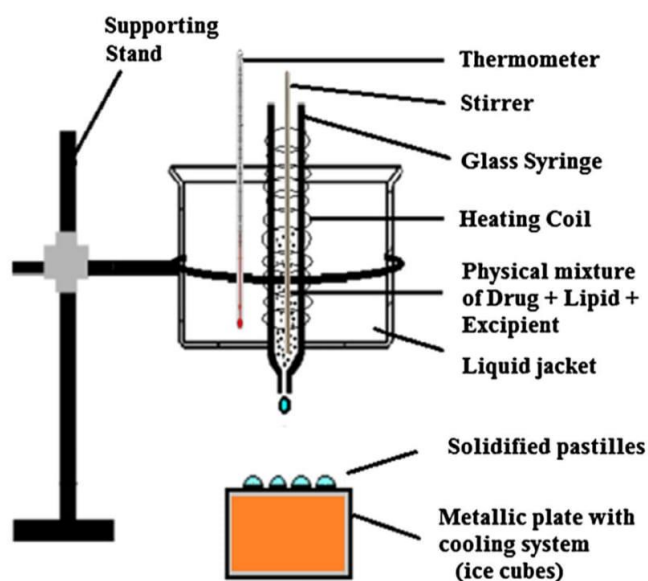


Figure 1: Schematic diagram of pastillation assembly.⁽⁴⁾

Pastilles are lipid-based formulation used to increase the solubility, dissolution rate and bioavailability of BCS class-II drug. Lipid which melts and resolidifies are of good choice in pastillation process. These are the solid discrete unit made by pastillation process. Drug delivery using lipid-based formulation is emerging dosage form due to versatile structural appearance of lipid excipients this are considered as valuable alternative. The apparatus used for the pastillation is also known as droplet solidification apparatus.⁵

MATERIALS AND METHODS

1. Materials

Diclofenac Sodium, Kolliphor HS 15 was gifted by BASF India, Poloxamer P188, Polyvinyl pyrrolidone 10000; Polyethylene glycol 400, Aerosil, KCl, Methanol was purchased from Loba Chemie, Mumbai.

2. Methods

3.1 Saturation solubility study

i) Diclofenac Sodium

Saturation solubility was carried out to determine the saturation concentration of Diclofenac Sodium in water. This study was conducted by the method proposed by Higuchi and Conors⁶. Excess quantity (200mg) of drug was taken in screw capped tubes with fixed volume (20 ml) of deionized water. It was shaken at 100 rpm at 37 °C for 48hrs on orbital shaker for equilibrium. After 48 hrs, the samples were withdrawn and filtered through 0.22µm membrane filter. The filtrate was suitably diluted and analysed at 281 nm by using UV spectrophotometer.

ii) Physical mixture

Saturation solubility of drug with polymer mixture was done to select the polymer for pastillation. Mixture of drug and polymer showing highest solubility was selected for the preparation of pastilles. Excess quantity of physical mixture of drug and solubilizer in 1:1 ratio was taken in screw capped tubes with fixed volume (20 ml) of deionized water. It was shaken at 100 rpm at 37 °C for 48hrs on orbital shaker for equilibrium. After 48 hrs, the samples were withdrawn and filtered through 0.22µm membrane filter. The filtrate was suitably diluted and analyzed at 281 nm by using UV spectrophotometer.

3.2 Dissolution test of Diclofenac Sodium: -

In-vitro release of Diclofenac Sodium was carried out using USP dissolution apparatus II (EDT-08L, Electrolab, India) using 900 mL of Phosphate buffer pH 6.8 dissolution medium at 50 rpm and 37 ± 0.5 °C for 90 min. Single dose of Diclofenac Sodium, 40 mg, was placed in muslin cloth and was tied to the paddle of apparatus. 900 ml of phosphate buffer pH 6.8 was used as a dissolution medium. Apparatus was operated at 37±0.5 °C with 100 rpm for 90 min. 5ml sample was periodically withdrawn at predetermined interval with replacement of equal quantity of preheated dissolution medium to maintain the sink condition. The samples were filtered using 0.45µm Whatman filter paper and analyzed by UV spectrophotometer at 281 nm.

3.3 Preparation of pastilles: -

Pastillation is the process in which the solid dispersion using the drug and the polymer is made. Previously weighed Diclofenac Sodium and Kolliphore HS 15 were mixed in 1:1 ratio by adding 500mg each and melted at 170-180 °C. Then this dispersion was placed in the glass syringe and then as the heat is applied by the heating coil then this hot molten

mass is allowed to fall drop by drop on the metallic plate with cooling system. Hot droplets were solidifying and form the pastilles⁽⁴⁾.

3.4 Evaluation of pastilles: -

i) Practical Yield: -

Total quantity of Diclofenac Sodium and Kolliphor HS 15 was considered as theoretical yield. Final quantity of pastilles after the completion of pastillation process was considered as practical yield. By using following formula and comparing the practical yield with theoretical yield the % practical yield was calculated. This was calculated to know the suitability of method.

$$\% \text{ Practical yield} = \frac{\text{Practical yield} \times 100}{\text{Theoretical yield}}$$

ii) Drug content: -

Solidified pastilles were triturated and placed in dry 100 ml volumetric flasks. Methanol (100 ml) was added to it and sonicated in an ultrasonic water bath for 10 min while shaking occasionally. The samples were filtered through 0.45µm filter, diluted appropriately with methanol and analysed for Diclofenac Sodium by UV spectrophotometer (UV 1800, Shimadzu, Japan) at 281 nm. Blank solution was prepared by similar treatment of placebo batches to avoid interference due to the presence of excipients.

3. Interaction study of drug with solubilizers

Interaction of Diclofenac Sodium with different solubilizers was studied by using FT-IR (IR Affinity 1S model) . It was based on the diffuse reflectance spectroscopy.

i) Fourier- transform infrared spectroscopy (FT-IR): -

Samples were mixed with potassium bromide and scanning from 4000-400 cm⁻¹. Spectrum of pure drug, solubilizer and pastilles were interpreted and compared to know any chemical interaction between them.

4. Solubility study of pastilles: -

Saturation solubility was conducted to determine the saturation concentration of Diclofenac Sodium pastilles in water. This study was conducted by the method proposed by Higuchi and Conors⁶. Excess quantity (200mg) of pastilles was taken in screw capped tubes with fixed volume (20 ml) of deionized water. It was shaken at 100 rpm at 37 °C for 48 hrs on orbital shaker for equilibrium. After 48 hrs, the samples were withdrawn and filtered through 0.22µm membrane filter. The filtrate was suitably diluted and analyzed at 281 nm by using UV spectrophotometer.

5. Dissolution test of pastilles: -

In-vitro release of pastilles was carried out to know any changes in the dissolution rate of drug following the pastillation. Weight equivalent to single dose of Diclofenac Sodium pastilles was calculated according to the drug contents was placed in muslin cloth and tied to the paddle of USP type-II dissolution test apparatus (EDT-08L, Electrolab, India). 900 ml of phosphate buffer pH 6.8 was used as a dissolution medium. Apparatus was operated at 37±0.5°C with 100 rpm for 90 min. 5ml sample was periodically withdrawn at predetermined interval with replacement of equal quantity of preheated dissolution medium to maintain the sink condition. The samples were filtered using 0.45µm Whatman filter paper and analyzed by UV spectrophotometer at 281 nm.

RESULTS AND DISCUSSIONS

1 Saturation solubility study: -

i) Diclofenac Sodium: -

Saturation concentration of Diclofenac Sodium in distilled water was found to be 11.12 µg/ml. This value is an indication of low solubility of the drug.

ii) Physical mixture of drug and polymer: -

It was found that, combination of Kolliphor HS 15 showed maximum saturation concentration of drug 15.01 µg/ml and hence selected for the preparation of pastilles.

Table 1: Saturation solubility of Physical mixture of drug and polymer

Sr. No.	Drug	Polymer	Concentration (µg/ml)
1	Diclofenac Sodium	Poloxamer P188	9.12
2	Diclofenac Sodium	Kolliphor HS 15	16.65
3	Diclofenac Sodium	Polyvinyl pyrrolidone 10000	8.96
4	Diclofenac Sodium	Polyethylene glycol 400	9.8

2 Dissolution study of Diclofenac Sodium: -

Pure Diclofenac Sodium showed 34.268% of drug release in 90 min. This may be attributed to its low aqueous solubility.

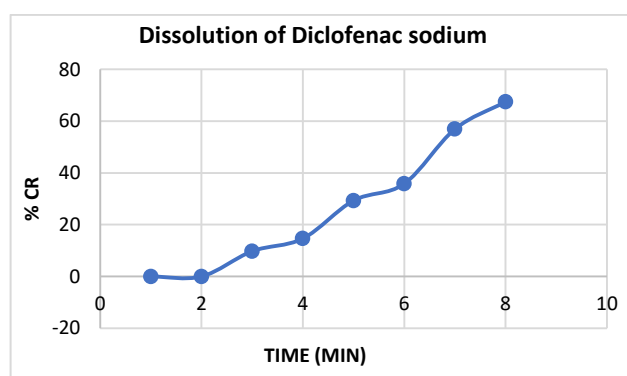


Figure 2: Dissolution profile of Diclofenac Sodium

3. Evaluation of pastilles: -

i) % yield: -

% practical yield was found to be 92% which suggests the suitability of this method for industrial or large scale.

ii) Drug content: -

Drug content was found to be 89.45% which is quite satisfactory suggesting the method used for preparation was suitable and reproducible.

4. Interaction study of drug with solubilizers

i) FT-IR of Diclofenac Sodium: -

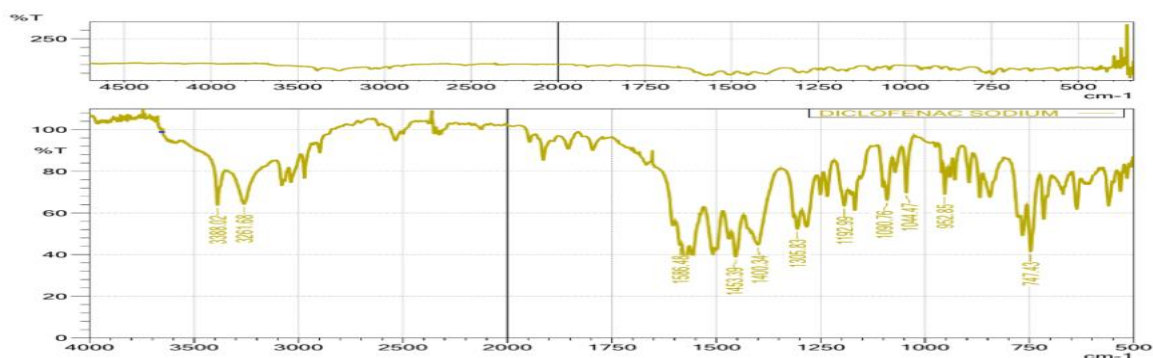


Figure 3: FT-IR spectrum of Diclofenac Sodium

After interpretation of FT-IR Spectrum of drug, it was concluded that all the characteristic peaks corresponding to the functional group present in molecular structure of

Diclofenac Sodium were found within the reference range, confirming its identity.

ii) FT-IR of Kolliphor HS 15: -

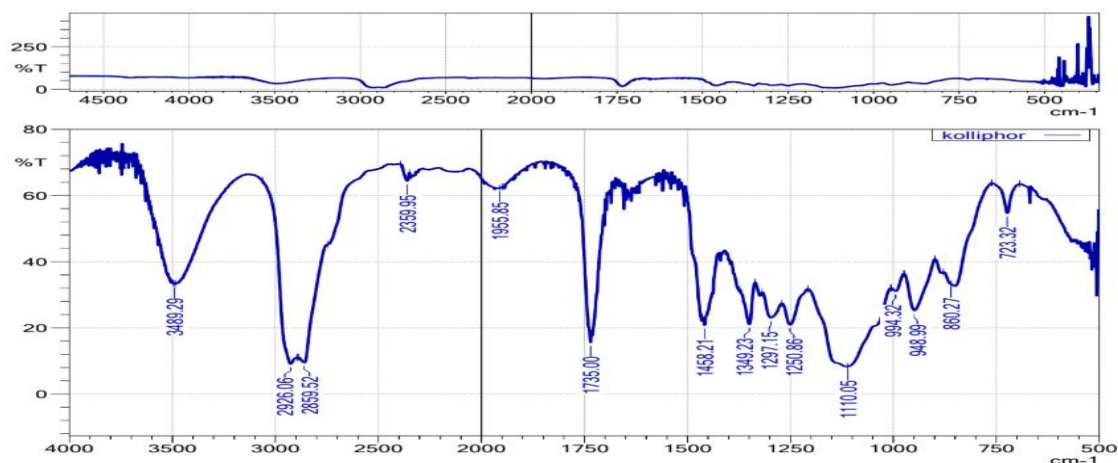


Figure 4: FT-IR spectrum of Kolliphor HS 15

After interpretation of FT-IR Spectrum of polymer, it was concluded that all the characteristic peaks corresponding to the functional group present in molecular structure of

Kolliphor HS 15 were found within the reference range, confirming its identity.

iii) FT-IR of Diclofenac Sodium + Kolliphor HS 15 physical mixture: -

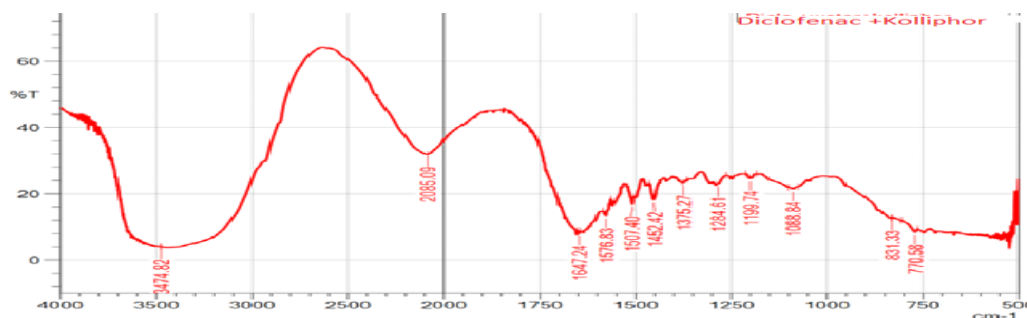


Figure 5: FT-IR spectrum of physical mixture of Diclofenac Sodium and Kolliphor HS 15

After interpretation of FT-IR Spectrum of Kolliphore HS 15 and its physical mixture with drug, it was concluded that all the characteristic peaks corresponding to the functional group present in molecular structure of Diclofenac Sodium

were not found intact within the reference range, confirming its reactivity with Kolliphore HS 15. This interaction further supports the selection of polymer.

FT-IR spectrum of Diclofenac Sodium pastilles

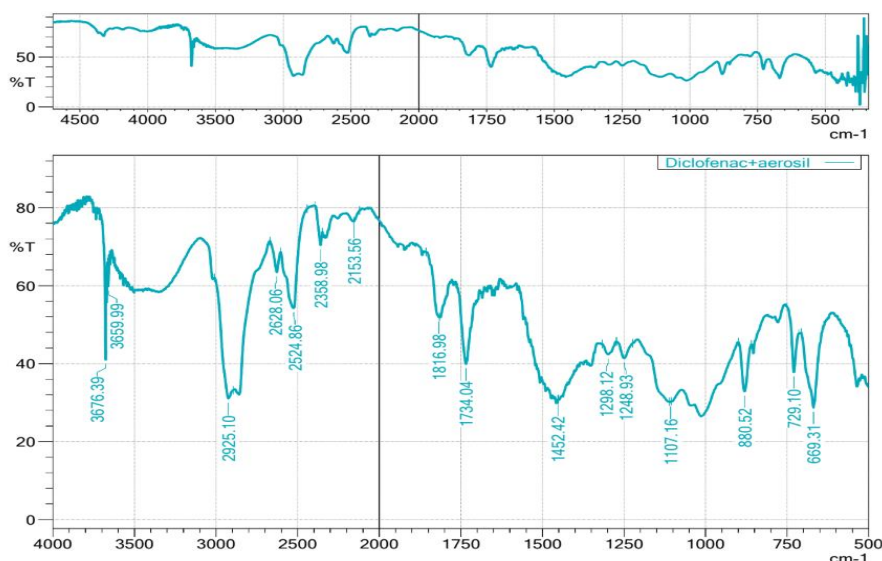


Figure 6: FT-IR of Pastilles of Diclofenac Sodium

FT-IR Analysis

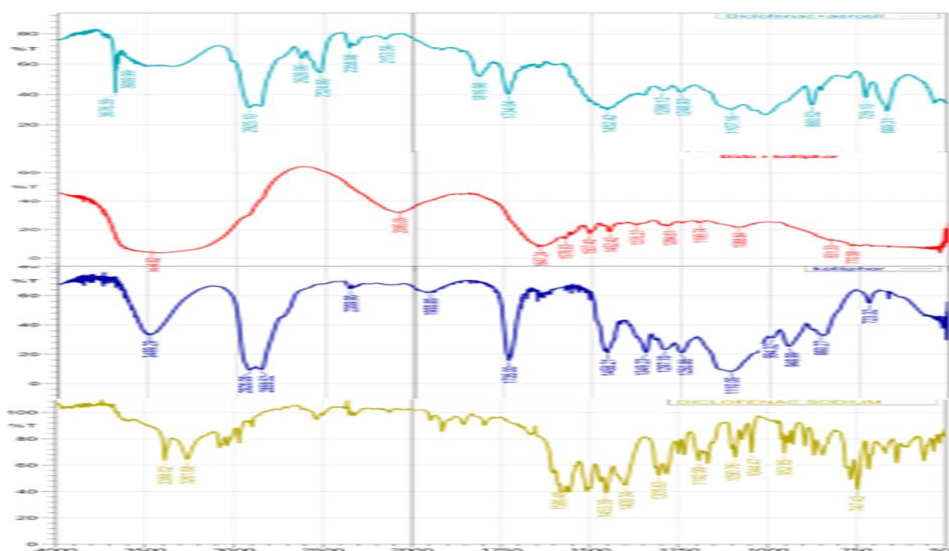


Figure 7: Overlay of all FT-IR spectra

Solubility study of Pastilles: -

Saturation concentration of Diclofenac Sodium from pastilles showed increased aqueous solubility. The saturation concentration of Diclofenac Sodium in water was found to be 17.89 µg/ml. This was almost 52.93 % increment of solubility.

Dissolution test of Diclofenac Sodium pastilles:-

Pastilles of Diclofenac Sodium showed increased drug release of 87.62% in 90 min. This is almost double as compared to pure drug. Enhanced dissolution may be attributed to the increased aqueous solubility of Diclofenac Sodium following the pastillation.

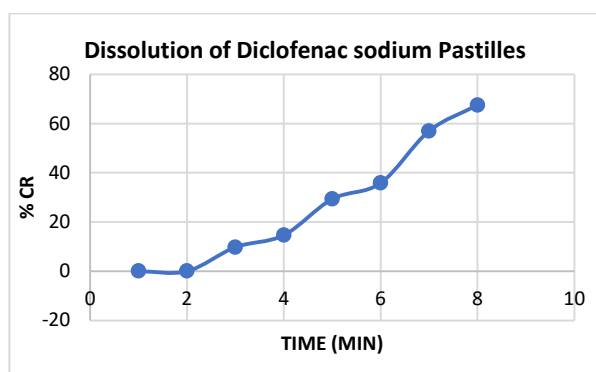


Figure 8: Dissolution of pastilles of Diclofenac Sodium.

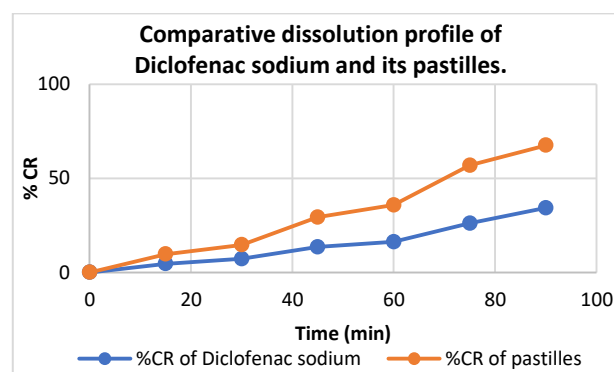


Figure 9: Comparative dissolution profile of Diclofenac Sodium and its pastilles.

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