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Technical Note

DEVELOPMENT OF DISSOLUTION MEDIUM FOR POORLY WATER SOLUBLE DRUG RACECADOTRIL

Lakshmana Prabu S*[1], Singh Tarunveer[2] and Dinesh Kumar C[2]

[1] Anna Unviersity Tiruchirappalli, Tiruchirapalli – 620 024. Tamilnadu, India.

[2] Manipal College of Pharmaceutical Sciences, Manipal, Karnataka – 576 104, India.

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ABSTRACT

A new dissolution medium was developed for the antidiarrhoeal drug, Racecadotril. The drug is poorly soluble in water; it is not official in any pharmacopoeia. In the present study was to develop a new dissolution medium for Racecadotril. The composition of the medium was selected based on the earlier information and solubility data of racecadotril at 37 ± 0.5º C. Solubility data revealed that water consisting of 3.0%w/v sodium lauryl sulphate could be a suitable dissolution medium. The discriminating power of the selected dissolution medium relative to other dissolution mediums was evaluated and the results further justified the usage of 3.0%w/v sodium lauryl sulphate in water as dissolution medium for racecadotril.

Keywords: *Racecadotril; Dissolution medium; Sodium lauryl sulphate; Tween 80*

INTRODUCTION

Racecadotril is chemically 2-[2-(Acetyl sulfanylmethyl)-3-phenyl-propanoyl] amino acetic acid benzyl ester[1], which is a prodrug of the enkephalinase inhibitor, thiorphan. It is used as an antidiarrhoeal. However, the drug is not official in any pharmacopoeia.

Developing dissolution methods for poorly soluble compounds has been a consistent challenge for the pharmaceutical scientists. Because of inherently slow dissolution, poorly soluble compounds are good candidate for developing *in vitro in vivo* correlations (IVIVCs)[2]. The use of dissolution testing as a quality control tool grew explosively in the decade of the 1970s. During the 80s the pharmaceutical industry began to develop a data base that connected the dissolution performance of oral, solid dosage form. The dissolution properties (extent and profile) of a finished dosage form should be monitored during product scale up. Assuming that a meaningful robust dissolution procedure has been developed, it can be a powerful tool to evaluate the impact of formula, process, equipment and site changes that may occur during product scale-up[3]. To determine appropriate dissolution conditions *a priori* in order to get an IVIVC is a topic of great Interest, Some progress has been made in identifying media to simulate the gastro intestinal milieu[4,5].

Drugs that are practically insoluble are of increasing therapeutic interest, but it is well recognized that they may present particular problems related to bioavailability when administered orally. Since their dissolution rate can be the rate-limiting step in the *in vivo* absorption process, there is a definite need for the development of an appropriate dissolution medium[6].

Approaches usually used in the design of a dissolution media for poorly water soluble drugs include; a) bringing about drug solubility by increasing the volume of the aqueous sink or removing the dissolved drug b) Solubilization of the drug by co-solvents[7-9], up to 40% and by anionic or non ionic surfactants added to the dissolution medium in post micellar concentrations c) alteration of pH to enhance the solubility of insoluble drug molecules[10-12].

In the present investigation, aqueous solubility of racecadotril containing co-solvents and surfactants were assessed to prepare a dissolution system, which satisfies sink conditions (sink condition refers to the excess solubility capacity of the dissolution medium). Commercial formulation containing racecadotril were tested and evaluated for assessing the discriminating power of selected dissolution medium.

EXPERIMENTAL

Materials

Racecadotril was a gift sample from Dr. Reddy's Laboratories Ltd, Hyderabad, India. Commercial brand of racecadotril capsules (Zedott®, Torrent Pharmaceuticals Ltd.) were purchased from the local market. Sodium lauryl sulphate and Tween 80 were procured from S.D. Fine Chemicals Mumbai, methanol and hydrochloric acid were procured from Qualigens Fine Chemicals, Mumbai. All the materials were of analytical reagent grade.

Methods

Solubility measurements were performed according to the method of Higuchi and Connors[13]. In brief, various aqueous solutions were prepared containing co-solvents or surfactants. 10 ml of these solutions were

***Correspondence :** slaxmanvel@gmail.com

taken into separate screw-cap test tubes. An excess amount of racecadotril was added to the test tubes. The screw-cap test tubes containing racecadotril with various co-solvents and surfactant mixtures were shaken at 37 ±0.5ºC for 24 h in a water bath. After shaking, the test tubes were kept for equilibration in an incubator at 37 ±0.5º C for 12 h. The solution was filtered through a 0.45□m millipore filter and the filtrate was analyzed spectrophotometrically at 231 nm against respective blank solutions.

Saturation Solubility: The standard way to affect the saturation solubility of drug in the dissolution media is to change the media, typically by adjusting the pH, adding a surfactant, or in rare cases, using non-aqueous solvents.

Generally baskets at 100 rpm are used for capsule[14]. Dissolution experiments were performed in commercial marketed formulation (label claim 100 mg) using a USP standard dissolution apparatus 1 (Electrolab model USP XXIII) at 37 ± 0.5º C at 100 rpm. The dissolution medium was 900ml of either water or a mixture of water and sodium lauryl sulphate (SLS) solution (1.0%w/v SLS in water, 2.0 % w/v SLS in water and 3.0 % w/v SLS in water), selected on the basis of solubility data obtained in the experiment. Samples (5 ml) of dissolution medium were withdrawn at different time intervals and filtered through a 0.45□m millipore filter. Same volume of fresh dissolution medium, maintained at 37 ±0.5ºC was added to maintain constant volume. The dissolution medium was analyzed for racecadotril using UV method as described above.

RESULTS AND DISCUSSION

In this present study an attempt was made to develop a dissolution medium for racecadotril, a poorly water soluble drug. Selecting the most appropriate medium for routine Quality control testing is based on discriminating capability, ruggedness, stability of the analyte in the test medium, and relevance to *in vivo* product performance wherever possible. Dissolution problems with poorly soluble compounds generally fall into two categories. First, extent of release is too low, i.e. one cannot get 100% of the dosage form dissolved. Second, rate of release is too slow, i.e. one cannot get dissolution fast enough for a convenient test. Understanding the physicochemical properties of the drug is crucial for determining the most effective strategy for enhancing dissolution. Profiling should be done in multiple dissolution media in order to characterize the pH susceptibility of the drug products. Suggested media include water, 0.1 N HCl and USP buffer at pH 7.5[3]. Solubility studies were performed in water, 0.1 N HCl and phosphate buffer pH 7.5, and the results are shown in Table 1. The results revealed that the drug is poorly soluble in the above media. Typically, the greatest enhancement in dissolution of poorly soluble compounds is made by changing the dissolution medium to increase compound solubility. Aqueous media without any surfactants are preferred, but aqueous media with surfactants may be used to increase the probability of establishing an *in vivo* relationship. Surfactants and pH changes are very effective way to increase solubility.

Table 1: *Saturation solubility of racecadotril in different media*

Media	Concentration* ± s.d (µg/ml)
Water	39.68 ±5.5
0.1N HCl	86.13 ±4.04
Buffer pH 7.4	101.13 ±1.35
0.2% SLS	103.63 ±5.12
0.5% SLS	349.88 ±8.32
1.0% SLS	774.86 ±6.14
1.25% SLS	813.63 ±3.25
1.50% SLS	833.63 ±7.24
2.0% SLS	898.0 ±6.24
3.0% SLS	960.35 ±5.37
0.5% v/v Tween 80 in water	63.63 ±2.57
1.0% v/v Tween 80 in water	87.38 ±3.58
5% v/v Methanol in water	94.88 ±3.41
10% v/v Methanol in water	119.88 ±4.12
20% v/v Methanol in water	137.38 ±2.48

**The results are mean of three readings (n=3)*

Two factors to consider when evaluating surfactants are cost and concentration needed. If the dissolution assay is to be run in a Quality Control setting, choosing an inexpensive surfactant will be important to keep overall assay costs down. Examples of inexpensive surfactants are sodium dodecyl sulfate or SDS (also referred to as sodium lauryl sulfate or SLS) for an anionic surfactant, cetyltrimethylammonium bromide or CTAB for a cationic surfactant, and the polysorbates or Tweens for a non-ionic surfactant[15]. Using a non-aqueous solvent mixture as a dissolution medium is discouraged; however, if an IVIVR (i*n vivo-in vitro* relationship) or IVIVC (i*n vivo-in vitro* correlation) is demonstrated that cannot be accomplished with a purely aqueous medium, an aqueous-organic solvent may be considered. The acceptability of such an aqueous-organic solvent media for dissolution media is unconventional. From a practical point of view, if such a medium is filled with the regulatory authorities, one will probably be expected to show that conventional tactics for getting adequate solubility and dissolution do not work[16].

In order to improve the solubility of racecadotril by considering the above information surfactants like SLS and tween 80 were added in various proportion in water, where as methanol was included in various proportion as co-solvent in the aqueous –organic solvent as dissolution medium. Solubility studies were performed in 0.2% w/v SLS, 0.5% w/v SLS, 1.0% w/v SLS, 1.25% w/v SLS, 1.5% w/v SLS, 2.0% w/v SLS and 3.0% w/v SLS, 0.5 % v/v tween 80, 1.0 % v/v tween 80, 5 % v/v methanol, 10.0% v/v methanol and 20 % v/v methanol in water. The solubility study results are shown in

Table 1. The results revealed that 3.0% w/v SLS in water showed maximum solubility of racecadotril when compared to other media. It was found that the maximum solubility was obtained with 3.0 % w/v SLS in water (960.35 □g/ml). From the above results, it was calculated that the solubility of racecadotril in 900 ml of 3.0 % w/v SLS in water was found to be approximately 10 times of the solubility to the original dose of racecadotril (100 mg). As 900 ml of 3.0 %w/v SLS in water was satisfying the sink conditions, it was considered to be a suitable dissolution medium for dissolution studies.

The comparative study of the dissolution rate of the marketed formulation in water and in different strengths of SLS (1.0 % w/v, 2.0 % w/v and 3.0 % w/v) solutions was carried out to justify the inclusion of SLS in the dissolution medium and the release study results are shown in Fig.1. The results indicated that the dissolution rate of racecadotril increased with increase in SLS content in dissolution medium and maximum dissolution was found in water containing 3.0 % w/v SLS. Addition of surfactant to the dissolution medium improves the dissolution of pure drug by facilitating the drug release process at the solid/liquid interface and micelle solubilisation in the bulk. The usage of water containing 3.0 % w/v SLS as the dissolution medium is justified by this data and could be used for routine *in vitro* dissolution testing of conventional racecadotril formulation.

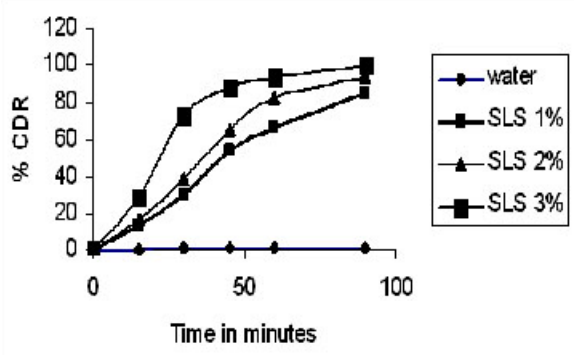

Fig. 1: *In vitro release of racecadotril from marketed product in different concentrations of SLS solutions*

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