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Research Article

EVALUATION OF INNOVATED FORMULA OF BISACODYL SUPPOSITORY FOLLOWING THE DISSOLUTION PROFILE AND STABILITY DATA USING DEVELOPED HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY METHOD

KAHTAN J HASSON, ESRAA G JABAR, IHAB I ALKHALIFA*

Department of Pharmacy, Al-Rasheed University College, Baghdad, Iraq. Email: dr_ihab75@yahoo.com

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ABSTRACT

Objective: Bisacodyl is a laxative drug used in the treatment of constipation, it is soluble in mineral acids, but it is practically insoluble in water. Therefore, it is very hard task to dissolve bisacodyl in alkaline medium so the objective of this study was the development of proper dissolution method for a new formulation of bisacodyl suppositories in a medium simulated to rectal region. Obviously, most of the bisacodyl suppositories preparation products will yield low percentages of dissolution in the alkaline medium of phosphate buffer pH 7.2.

Methods: Preparation inclusion complex of bisacodyl with the solubilizing agent beta-cyclodextrin then incorporated in a suppository base. The quantitative analysis of bisacodyl in suppositories was carried by a developed and validated high-performance liquid chromatography method.

Results and Discussion: Of the dissolution rates for the innovated formulation of bisacodyl suppositories were in average of 97.5% and the stored suppositories of this formulation maintained their specified physical and chemical properties along the real stability study.

Conclusion: The application of the inclusion complexation technique of bisacodyl with beta-cyclodextrin in the production of suppositories enhances the dissolution rate and improves the stability of suppositories performance.

Keywords: Dissolution, Beta-cyclodextrin, Stability, High-performance liquid chromatography method.

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INTRODUCTION

Bisacodyl is used in the treatment of constipation. Its mechanism of action has been discussed by enhancing the bowel evacuation which contributed to the effect of the hydrolytic product (deacetylated compound) of bisacodyl [1]. It has been found that the laxation effect in oral administration occurs within about 7 h; however, it takes not more than 20 min in case of suppositories application of bisacodyl, this indicated the local effect of bisacodyl in motivation of colon [2]. The dissolution test of bisacodyl suppositories has not officially mentioned yet in B.P or USP. Therefore, the preliminary aim of this work was to establish a proper system for the dissolution and determination method of analysis. In general, the dissolution medium is selected to simulate the actual site of absorption in the human body and it is a colonic region in case of suppositories dosage forms, where the pH is between 7.2 and 7.5 [3]. Bisacodyl substance is practically insoluble in water and soluble in dilute mineral acid as described by B.P 2013; therefore, it has poor solubility in alkaline medium as it has been selected for dissolution medium (phosphate buffer pH 7.2) to be similar to the site of action of the suppositories (colon). In general, the addition of surfactants (sodium lauryl sulfate [SLS]) and Tween 80 to the dissolution acts as solubilizing agents and obviously will enhance the dissolution medium of poor water-soluble drugs [4]. The USP 38 has used SLS in the dissolution medium of sustained-release tablet; however, this application is not practically recommended for suppositories dosage forms. Some workers [5,6] reported the use of solubilizing agents to enhance the dissolutions of the drugs by incorporation of polyethylene glycol 400 or one of the surfactants SLS or Tween 80 in the formulation of suppositories, but it leads to low physical stability of the suppositories and there is a probability of mucous membrane irritation due to SLS application in the rectal region.

In this work, an attempt to use beta-cyclodextrin as a solubilizing agent by forming solid inclusion complex with the bisacodyl and incorporated in the suppository base. Beta-cyclodextrin is a cyclic derivative of starch prepared by partial enzymatic hydrolysis of starch (maltodextrin); it is safe in drug formulation and used in different dosage forms [7-9].

For stability study of the innovated formula, there was a need for stability-indicating method of analysis to assure specificity and sensitivity in analysis of stored bisacodyl suppositories. The published ultraviolet (UV) method [10] and the high-performance liquid chromatography (HPLC) method [11] for the determination of bisacodyl in a dosage form as tablet were found not suitable for stability work. Therefore, an HPLC method of analysis of bisacodyl suppositories was developed in this paper to follow the stability of bisacodyl suppositories on storage.

METHODS

Bisacodyl B.P, beta-cyclodextrin and suppositories base of semi-synthetic glycerides solid (DUB PP DL-France), HPLC apparatus (Cecil Co., England), attenuated total reflection infrared (IR) spectrophotometer (Bruker Co., Germany), melting point tester type SSP, suppository hardness tester SBT2, and suppository disintegration tester (Erweka, Germany), all are supplied in R&D Lab of SAFA Co. for Pharmaceutical Industries, Baghdad.

Preparation of suppositories

The normal routine manufacturing process of bisacodyl suppositories in SAFA Pharmaceutical Industry (Baghdad) is by incorporation of the measured amount of bisacodyl powder in sufficient quantity of suppository base (DUB PP DL-France) previously melted in small stainless steel mixer, fixed at 40°C with continuous mixing for 15 min; then, the mass was poured in plastic sheet molds for suppositories to contain 10 mg of bisacodyl in each suppository of total weight 1.7 g (F1). The innovated formula (F2) was prepared to contain 10 mg of bisacodyl powder mixed with beta-cyclodextrin to form a solid dispersion in a molar ratio of 1:1. The powder mixture is then gronded

by high-speed grinder and incorporated in a melted suppository base to be manufactured as suppositories.

IR spectrophotometry
The effect of β-cyclodextrin on the nature of bisacodyl powder in the formation of inclusion complex by solid dispersion was studied by IR spectrophotometry.

Hardness and melting test
The prepared suppositories were physically tested for melting point, hardness, and disintegration using Erweka apparatus.

HPLC quantitative analysis
The quantitative analysis of bisacodyl suppositories on assay and dissolution was determined by a developed HPLC technique. The HPLC method included the using of reversed-phase mode of chromatography with the following conditions; column of C18, 25 cm length and 5 μm particle size, the mobile phase was consisted of a mixture of acetonitrile and buffer solution (70:30), the buffer solution was prepared from sodium citrate solution 0.05 M, adjusted to pH 7.0 with diluted sodium hydroxide solution; the flow rate was 1 ml/min and the UV detection at 230 nm.

Dissolution test
It consists of a basket-type apparatus with rotation speed 75 rpm and 500 ml of dissolution medium using phosphate buffer (0.05 M), pH 7.2, procedure; dissolution operation was carried for 1 h, at the end time of dissolution test, sample of dissolution medium was withdrawn, filtered, and applied to HPLC analysis.

Evaluation of the new prepared formula of bisacodyl suppositories
The newly prepared formula of bisacodyl suppositories (F2) was evaluated by comparing the obtained analytical data in dissolution profile which is constructed by the determination of dissolution percentage of bisacodyl in suppositories at intervals with that of other commercial products of bisacodyl suppositories.

Stability study
Samples of prepared bisacodyl suppositories (F2) in their packing were stored in a stability chamber which was fixed at room temperature (30°C and 65% RH of Iraq region), and the physicochemical properties of the suppositories were examined in intervals during the period of storage which lasts for 2 years as a real stability study program.

RESULTS AND DISCUSSION

The IR spectrum of bisacodyl
The IR spectrum of bisacodyl before and after complex formation with beta-cyclodextrin is shown in Figs. 1-3.

The characteristic peaks of bisacodyl with frequencies 1752.6 cm^{-1}, 1201.2 cm^{-1}, and 515 cm^{-1} are still present in the IR spectrum of the complex with beta-cyclodextrin indicating incomplete inclusion due to physical mixing which differs from bending process where water is introduced. However, the bisacodyl complex showed more solubility in water due to the hydrophilic effect of hydroxyl group (frequency 3285.78 cm^{-1}) in the solid inclusion complex with beta-cyclodextrin.

Physical properties
Two different formulations of bisacodyl suppositories (F1 and F2) were tested and the results are shown in Table 1.

These results indicate no difference in the physical properties, particularly the melting point, and disintegration times with the new formulation (F2) which includes the additive beta-cyclodextrin.

Validation of HPLC method
The developed HPLC method was applied for quantitative analysis of bisacodyl suppositories 10 mg in 500 ml of dissolution medium, the resulted chromatogram showed a retention time about 9 min for bisacodyl and the efficiency of the column was more than 5000 number of plates (Fig. 4). The relationship of peak areas and the different dilutions of bisacodyl solution in a range (0.5–3.0 mg/100 ml) showed a straight-line plot with a correlation coefficient equal to 0.998 which indicated high precision of analysis (Fig. 5).

Assay and dissolution tests
The chemical assay and dissolution test results of the prepared bisacodyl suppositories and other commercial products are shown in Table 2, and the competitive dissolution profiles of these products are shown in Fig. 6.

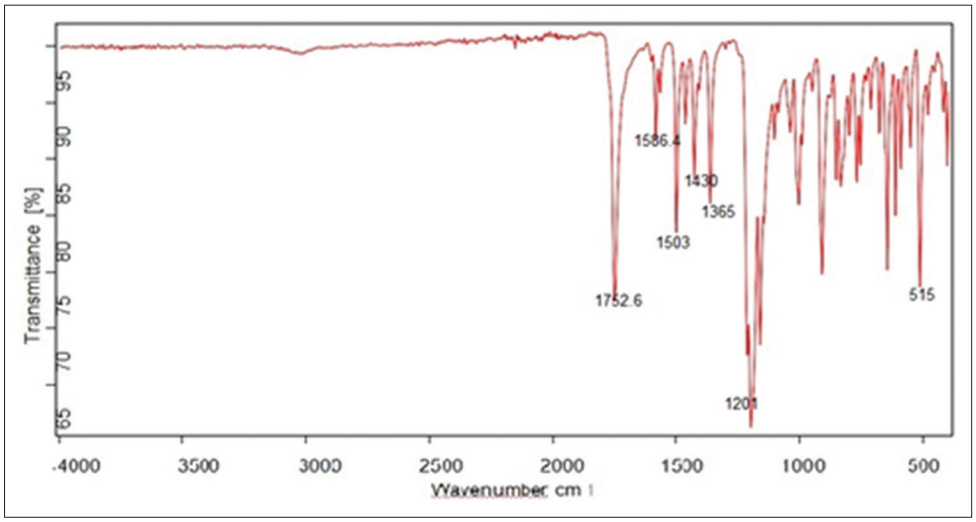

Fig. 1: Infrared spectrum of bisacodyl pure

Table 1: Physical tests of prepared bisacodyl suppositories

Formula	Bisacodyl powder	Beta-CD	Base up to	Hardness	Melting point U-tube	Disintegration test B.P method
F1	10 mg	-	1.7 g	1.2 kg	36.0°C	Pass
F2	10 mg	30 mg	1.7 g	1.2 kg	36.5°C	Pass

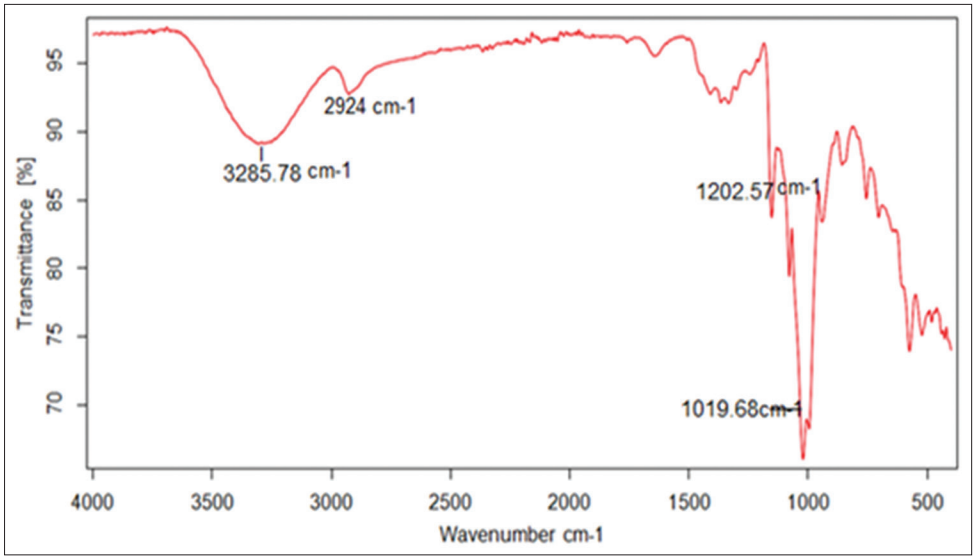

Fig. 2: Infrared spectra of beta-cyclodextrin

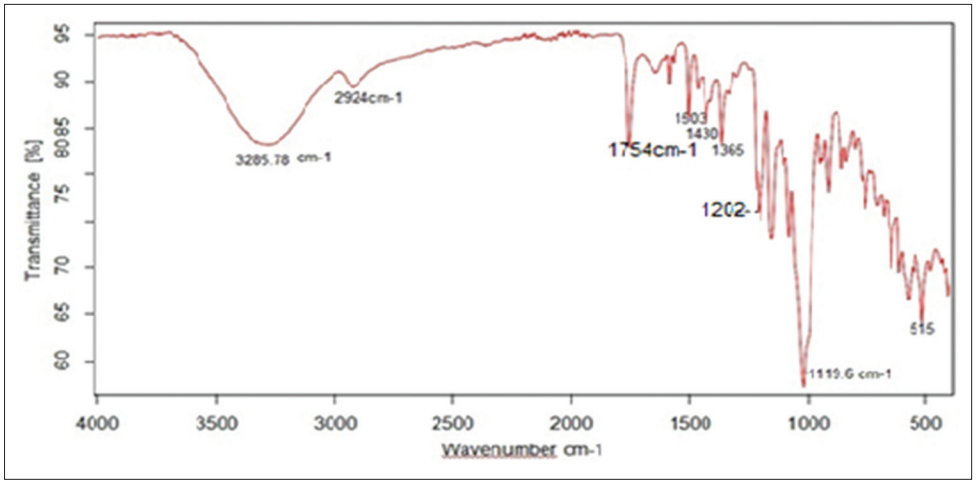

Fig. 3: Infrared spectra of beta-cyclodextrin with bisacodyl complex

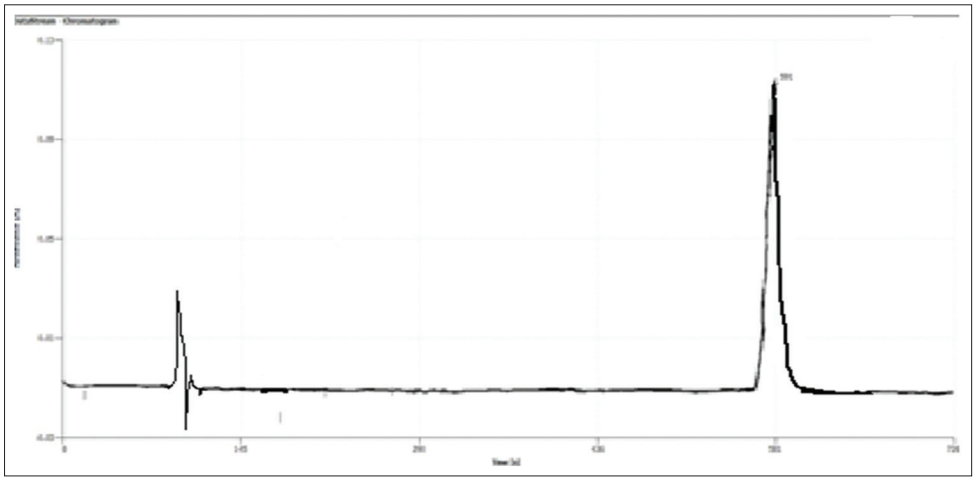

Fig. 4: The high-performance liquid chromatography chromatogram of bisacodyl in suppository

The innovated formulation of bisacodyl suppository (F2) showed the highest rate of dissolution (97.2%) within the applied commercial products of Iraqi market. The results of dissolution profiles, on the other hand, indicated that the innovated formulation was highly soluble in dissolution medium, while some commercial products were less than the required limit (general limit of USP is not <70%).

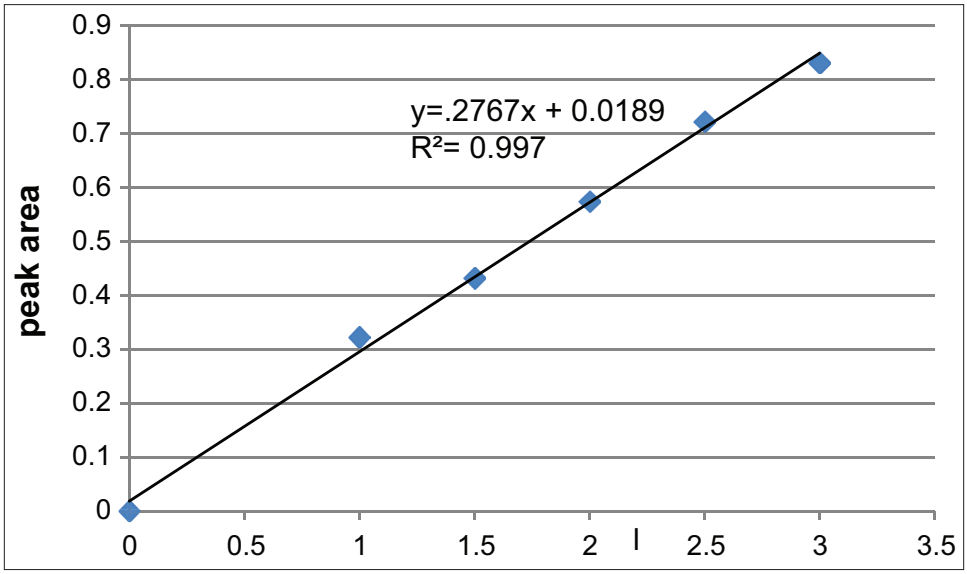

Fig. 5: The straight-line relationship for bisacodyl concentrations and their peak areas

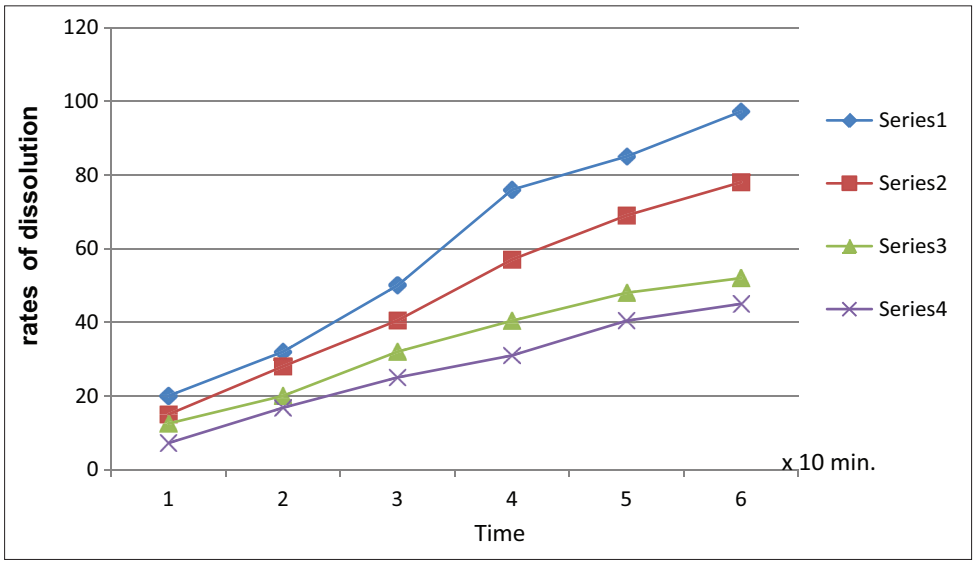

Fig. 6: The dissolution profiles of bisacodyl suppositories of different products; series 1 – innovated formula (F2), series 2 – Dulcolax supps., series 3 – Laxal supps., series 4 – Safalax supps. (F1)

Table 2: Dissolution rates after 1 h of the prepared and commercial bisacodyl suppositories

Bisacodyl suppository	Initial assay (%)	Dissolution rates/phosphate buffer pH 7.2 after 1 h (%)
Prepared F2	100.1	97.2
Prepared F1	100.05	45
Laxal supps., Pharma Life Co.	100.2	52
Dulcolax, Sanofi Co.	100.5	76

The stability testing

The physical properties of the suppositories along the 2 years of storage were within the specified conditions; in addition, the HPLC assay of bisacodyl suppositories at the past month of storage for five samples gave average 99.2% of bisacodyl relative to the labeled amount and the relative standard deviation of these five samples was 0.3%. The HPLC chromatogram of the analysis for stored samples of innovated formula did not show any secondary peak rather than bisacodyl peak, indicating the absence of any sign of degradation.

CONCLUSION

In the dissolution medium of phosphate buffer 0.05 M and pH 7.2, most of the different manufacturing products of bisacodyl suppositories were characterized by low percentage of dissolution rates due to low solubility of bisacodyl in alkaline medium. However, the use of beta-cyclodextrin in the formulation of suppositories was contributed to high enhancement in the rate of dissolution of bisacodyl. In addition, the developed HPLC method of analysis in this work was highly precise

and could carry the accurate analysis of stored samples of bisacodyl suppositories, indicating high stability of their innovated formulation.

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AUTHORS' CONTRIBUTIONS

Kahtan J Hasson designed and performed the formulation and did the quantitative analysis of the drug formula by a developed and validated HPLC method; moreover, he wrote the manuscript and supervised the work, Esraa G Jabar carried out biopharmaceutical kinetic study, Ihab I Alkhalifa reviewing and editing the final manuscript and as the corresponding author for submitting the article to the journal for publication. All authors discussed the results and commented on the manuscript.

CONFLICTS OF INTEREST

The authors declare that there exist no conflicts of interest regarding the publication of this paper.

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