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Formulation and evaluation of Diphenhydramine hydrochloride and Ibuprofen soft gelatin capsules

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ABSTRACT

The present invention provides a new composition for treating pain-associated sleep disturbances, especially shortened sleep duration, comprising ibuprofen and diphenhydramine hydrochloride. In the present work the soft gelatin capsules were formulated comprising 25 mg diphenhydramine hydrochloride and 200 mg ibuprofen using polyethylene glycol 400, propylene glycol, potassium hydroxide and purified water. The prepared soft gelatin capsules were evaluated for weight variation test, assay, dissolution and disintegration. The capsules had a fill weight of $550 \pm 5\%$, Disintegration time of 5-6 minutes and showed 97.00% to 99.50% of labeled amount of ibuprofen and diphenhydramine hydrochloride indicating uniformity in drug contents. The capsules containing 75 mg/capsule of propylene glycol released 99.40% of diphenhydramine hydrochloride and 99.70% of ibuprofen at the end of 60 minutes. Thus, it may be concluded that soft gelatin capsules of diphenhydramine hydrochloride and ibuprofen could be successfully prepared with existing technology and machinery which have a commercial viability and enhance patient compliance with improved bioavailability.

Key words: Capsule, soft gelatin, diphenhydramine hydrochloride, ibuprofen

INTRODUCTION

Soft gelatin capsules are the formulations which are formed, filled and sealed in one continuous operation. Softgels offer several advantages like versatile size, shape and elegance, tamper proof, content uniformity etc. Several advantages of soft gelatin capsules derive from the fact that these contain the active ingredient in solution, suspension or emulsion. This will inherently lead to better absorption of the active ingredient as compared with delivery of a tablet or a powder and patients find it easier to swallow capsules than tablets (Leon Lachman 1991). This preference has promoted pharmaceutical manufactures to market the product in capsule form (Gilbert S Banker et al 1995). The present invention provides a new composition for treating pain-associated sleep disturbances, especially shortened sleep duration, comprising ibuprofen and diphenhydramine hydrochloride (Cook GD et al 2002). Soft gelatin capsules shell was prepared using gelatin and glycerin as plasticizer. Capsules fill solution was prepared by using antihistaminic drug diphenhydramine hydrochloride and analgesic drug ibuprofen and was dissolved in hydrophilic solvent PEG 400. The capsules were evaluated for their ability to release drugs with in 60 minutes.

MATERIALS AND METHODS

Ibuprofen USP, Diphenhydramine hydrochloride USP, polyethylene glycol (PEG) 400, propylene glycol, potassium hydroxide were obtained as gift sample from Strides Arcolab Ltd, Bangalore. All the chemicals and reagents used in the study were of analytical grade.

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Preparation of Fill Solution

Drug fill solution was prepared by accurately weighing required quantities of ibuprofen and diphenhydramine hydrochloride along with various excipients as shown in Table 1. PEG 400 was collected into a stainless steel vessel. Potassium hydroxide was dissolved in purified water and transferred into PEG 400 portion. Ibuprofen was dissolved into PEG 400 and potassium hydroxide mix under continuous stirring till clear solution was obtained. Diphenhydramine hydrochloride in small quantities was added under continuous stirring to above mixture and continued the stirring until the solution becomes clear (Gabriele R 2003).

Table 1: Composition of Soft Gelatin Capsules (Quantities/capsules in mg)

Ingredients (mg)	Formulations Code			
	Fn-1	Fn-2	Fn-3	Fn-4
Ibuprofen USP	200	200	200	200
Diphenhydramine hydrochloride	25	25	25	25
PEG 400	290	275	225	200
Potassium hydroxide pellets	20	25	25	25
Propylene Glycol	-	-	50	75
Purified water	15	25	25	25

Preparation of Gelatin Shell

Gelatin shell was prepared using glycerin (25%), gelatin (35%) and purified water (40%). Glycerin along with purified water was mixed in shell preparation vessel by vacuum and the mixture was then heated to a temperature of 80°C. Once temperature was achieved, gelatin loaded into the shell preparation vessel by vacuum and completely mixed to get a uniform mixture. Vacuum was applied to remove air bubbles from the gelatin paste. Gelatin paste was then unloaded into preheated gelatin tanks maintained at 57°C to 60°C during the encapsulation process (Gabriele R, 2003).

Encapsulation

Encapsulation of fill solution into gelatin paste was done using rotary die machine (Arbes tools, Mumbai). Light mineral oil was used for machine lubrication. Capsules were dried for 48 hours at 30°C and 18% relative humidity. Wiping of capsules was done using Kimberly clothes to remove the adhering oil on to the capsules used for the purpose of lubrication during encapsulation. Wiped capsules were then subjected to inspection manually for removal of physical rejects like damaged or improperly filled capsules (Aulton MV 2004 and Drs Ervin Douwes 2003).

EVALUATION OF SOFT GELATIN CAPSULES

Drug Content

Drug content was determined by opening ten capsules and the fill solution equivalent to 12.5 mg of diphenhydramine hydrochloride and 100 mg of ibuprofen were weighed and transferred into 50 ml volumetric flask. 25 ml of pH 7.2 phosphate buffer (200 mM) was added into above volumetric flask. Sonicated and diluted to the volume with pH 7.2 phosphate buffer. Further 5 ml of the above solution was diluted to 25 ml with pH 7.2 phosphate buffer (200 mM). Finally drug content was estimated

using HPLC (Agilent Technologies) at 220 nm (Mobile phase: 600 ml pH 7.2 phosphate buffer and 400 ml Acetonitrile, Column: Inertsil pH-3, Flow rate: 1 ml/minute, Injection volume: 5 µL, Column oven temperature: 25°C and Runtime: 14 minutes) (USP 2007).

Disintegration Test

Disintegration test was performed by placing six capsules into the basket-rack assembly of the apparatus and discs were placed in each tube. The temperature of water inside the beaker was maintained at 37±5°C. Time in minutes was recorded at which last capsule of 6 capsules; disintegrate completely except fragments from the capsule shell.

Dissolution Study

Drug release study was carried out using USP dissolution rate test apparatus-I (Electrolab). The study was carried out at 37±5°C and 100 rpm for 60 minutes in 900 ml of pH 7.2 phosphate buffer after placing one capsule in each basket. After specified time interval, 10 ml of sample was withdrawn from midway between surfaces of the media and top of the rotating paddle. The sample was filtered through 0.45 µm filter and the drug contents were estimated using HPLC (Agilent Technologies) at 220 nm (Mobile phase: 600 ml of pH 7.2 phosphate buffer and 400 ml Acetonitrile, Column: Inertsil pH-3, Flow rate: 1ml/minute, Injection volume: 5 µL, Column oven temperature: 25°C and Runtime: 14 minutes).

RESULTS AND DISCUSSION

Table 2 shows the data obtained from the evaluation of soft gelatin capsules. The fill weight was found to be 550± 5%, Disintegration time was 5-6 minutes and showed 97.00% to 99.50% of labeled amount of ibuprofen and diphenhydramine hydrochloride indicating uniformity in drug contents. Drug releases from Fn-1 were 56% for ibuprofen and 46% for diphenhydramine hydrochloride at the end of 60 minutes. This was due to improper solubilization of ibuprofen in PEG 400 and diphenhydramine hydrochloride in purified water (Drs Ervin Douwes 2003). Potassium hydroxide and purified water were increased to 25 mg/capsule each in Fn-2, showed drug releases of 92% for ibuprofen and 54.30% for diphenhydramine at the end of 60 minutes (Kato et al 2003). This showed potassium hydroxide, an alkali in higher concentration was required to solubilize ibuprofen in PEG 400 but purified water slightly increased the release of diphenhydramine hydrochloride. Since both Fn-1 and Fn-2 showed less release of diphenhydramine, propylene glycol as a cosolvent for diphenhydramine was incorporated in Fn-3 and Fn-4 as further increase in purified water caused leakage of capsules. Formulation-3 (Fn-3) showed better release of diphenhydramine hydrochloride but was less than 90%. So propylene glycol concentration was further increased in Fn-4 to 75 mg/capsule to completely solubilize diphenhydramine hydrochloride. Fn-4 showed 99.70% of Ibuprofen and 99.40% of diphenhydramine hydrochloride release

Table 2: Data obtained from Evaluation of Soft gelatin capsules.

Capsules	Fill weight(mg)	Disintegration Time	Drug content (%)		Drug release at end of 60 minutes (%)	
			Ibuprofen	Diphen- hydramine	Ibuprofen	Diphen- hydramine
Fn-1	550± 5%	5minutes 15 sec	98.00	99.50	56.00	46.00
Fn-2	550± 3%	5minutes 35 sec	97.00	97.90	92.00	54.30
Fn-3	550± 1%	5minutes 30 sec	98.40	97.00	93.20	76.80
Fn-4	550± 5%	5minutes 25 sec	99.50	98.70	99.70	99.40

at end of 60 minutes as both were completely solubilized in fill solution.

CONCLUSION

In conclusion it can be said that, the formulation (Fn-4) containing 75 mg/capsule of propylene glycol showed maximum drug release, hence this formulation can be useful for treating pain-associated sleep disturbances, especially shortened sleep duration. Soft gelatin capsules of diphenhydramine hydrochloride and ibuprofen could be successfully prepared with existing technology and machinery which have a commercial viability and enhance patient compliance with improved bioavailability.

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