Jaya raja Kumar/J. Pharm. Sci. & Res. Vol. 6(8), 2014, 282-284

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

Formulation and Evaluation of Sustained Release Ambroxol Hydrochloride Microsphere Enriched Syrup

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Abstract

The main objective of the present work is to formulate taste masked microspheres enriched syrup of ambroxol hydrochloride by an o/w emulsion solvent evaporation method. Such taste-masked formulations have been found to improve the quality of treatment in patients. Ambroxol hydrochloride microspheres help to protect the gastric mucous membrane from drug irritation and to mask its taste. The prepared microspheres enriched syrup were evaluated for particle size, effect of drug and polymer ration and volume of dispersed phase, percentage yield, incorporation efficiency, pH, viscosity, scanning electron microscopy and in vitro drug release. The microspheres produced exhibited good encapsulation efficiencies and rheological properties. The maximum percentage yield of microsphere is around 85.31% and viscosity is 31000 cps. The mean diameters of microspheres were found in range between 4µm to 14µm. The results of optimized formulations showed a narrow size distribution and smooth surface. In-vitro release showed 72.3% drug release after nine hours.

Key word: Microspheres enriched syrup, Viscosity, SEM.

INTRODUCTION

Ambroxol is a metabolite of bromohexine which possess mucokinetic and secreteolytic properties. It is used in the treatment of respiratorytract disorders such as chronic bronchitis and management of cough. Adverse effects produced suchas gastrointestinal disorder, headache, dizziness, sweating, rhinorrhoea, lacrymation and allergic reactions. Due to short biological half-life (4-6 hr), frequent daily dosing (2-3 times) of Ambroxol hydrochloride is required[1]. Therefore its formulation inSR microspheres is advantages.The simplest and least expensive way tocontrol the release is to dispense it with in an inertpolymeric matrix[2]. Bitter after taste of many drugs which are orallyadministered often contributes to patient non-compliancein taking medicines. Unfortunately, majority of the drugshave a natural bitter taste that can create a burning feelingin the throat or in the mouth; many active ingredientssuch as antibiotics possess a strong unpleasant taste[3].Administration of bitter drugs orally with acceptablelevel of palatability is important in case of pediatric andgeriatric patients. Thus elimination or reduction of bitternessis an important parameter of product evaluation inoral pharmaceutical formulations. Proven methods forbitterness reductions have resulted in improved palatabilityof oral pharmaceutical formulations. Various techniqueshave been developed to improve taste, such as polymeric coating technique[4], complexation using cyclodextrins[5]and ion-exchange resin[6-8], using known coating orencapsulation[9] processes with very limited success. Ambroxol syrup is marketed in many countries worldwide for pain relief for sore throat. The local anaesthetic action of ambroxol, a sodium channel blocker, might be effective to relieve symptoms due to inflammation[10-12].

MATERIALS AND METHODS

MATERIALS

Ambroxol hydrochloride was generously supplied as a gift sampleby Alembic Ltd. Vadodara, India. Ethyl cellulose and PVP was obtained from Essex, UK, monobasic sodium phosphate and dibasicsodium phosphate Sigma Aldrich, Germany.

METHOD

Preparation of microspheres

The microspheres containing drugs were prepared by quasi emulsion solvent diffusion method using different drug and polymer ratio as shown in Table 1. The inner phase, ethocel and drug were dissolved in dichloromethane, ultra sonication for 10 min. The outer phase prepared by dissolving PVA in distilled water at 40ºC for 5 min. The inner phase is cooled then poured drop wise into outer phase. The resultant mixture was stirred by magnetic stirrer for 120 min at 25ºC, and filtered to separate the microspheres. The microspheres were dried in an air heated oven at 40 °C, and weighed to determine the yield.

Preparation of microsphere enriched syrup

Weight of microspheres added in the syrup formulation is equivalent to 30 mg of ambroxol hydrochloride, calculated on the basis of assay value. Microspheres prepared above were mixed separately with all the ingredients shownin Table 2. Buffers like monobasic sodiumphosphate and dibasic sodium phosphate were addedto adjust the formulation to pH 7. A sweetening agent, aspartame and vanilla added as a flavoring agent to all the formulation to improve the palatability.

Table 1: Composition of microsphere

Drug ratio (mg)	Polymer ratio (mg)	DCM Solvent (mL)	Yield
30	100	10	85.03±1.52
60	100	10	68.45±1.08
90	100	10	70.61±1.75
30	100	10	85.31±1.41
30	200	10	80.12±1.02
30	300	10	79.46±1.59
30	100	10	85.02±1.12
30	100	20	82.47±1.76
30	100	30	77.05±1.48

Table 2: Composition of microsphere enriched syrup

Composition (% w/v)	F1	F2	F3	F4
Microspheres (ambroxol HCL equivalent)	0.03	0.03	0.03	0.03
Sodium CMC	0.5	1	2	3
Sucrose	33.0	33.0	33.0	33.0
Monobasic sodium phosphate	0.04	0.04	0.04	0.04
Dibasic sodium phosphate	0.42	0.42	0.42	0.42
Sodium benzoate	0.2	0.2	0.2	0.2
Vanilla	q.s	q.s	q.s	q.s
Water (q.s)	Up to 100	Up to 100	Up to 100	Up to 100
pH	6.9	7.0	7.0	6.9

Particle size studies:

Particle size analyses were performed on microspheres by optical microscopy (DN-117M, USA). The results are the average of three analyses. The values (*d*50) were expressed for all formulations as mean size range.

Scanning electron microscopy:

The morphology and size of microspheres were observed by scanning electron microscopy. Prepared microspheres were coated with gold and studied by scanning electronmicroscopy (Phenoworld) under vacuum at room temperature.

Determination of pH

The pH of the solution and gel was determined using a calibrated pH meter. The readings were taken for average of 3 samples**.**

Viscosity Studies

The rheological studies were carried out using Brookfield programmable DVII+ Model pro II type (USA). The viscosity of microspheres enriched syrup and the solution were determined at different angular velocities (0.5, 1, 2, 2.5, 4, 5, 10, 20...to 50 rpm) and average of two reading was used to calculate the viscosity.

***In vitro* drug release study**

Microspheres enriched syrup equivalent to 30 mg of ambroxol hydrochloride were transferred to the vessels and subjected to dissolution studies using USP 24 apparatus type II (Paddle method) at 50 rpm/min with 900 ml of dissolution medium at 37.5 ± 0.1 °C for 9 hr. at 50 rpm. 10 ml of sample was withdrawn after every half hour, and was replaced with an equal volume of fresh dissolution medium. Collected samples were analyzed at 257 nm by spectrophotometrically. Dissolution data for microspheres in different dissolution medium like 0.1N HCl and pH 6.8 phosphate buffers are used.

RESULT AND DISCUSSION

Viscosity is the resistance to gradual deformation by shear stress. Viscosity is an important parameter in rheology of syrup. If the formulation is viscous enough, it may avoid particle aggregation and delay the drug release for longer period of time which may help in the sustained release of drug delivery. The shear stress increases, the viscosity decreases (0.5, 1, 2, 3% SCMC) as shown in figure 1, However 2% and 3% SCMC not suitable for patients.

Microspheres prepared with different ratio of DCM were irregular in shape, hard and rough in texture. The sizes of the drug loaded microsphere prepared with higher ratio of ethocel were larger and not uniform. The irregularity and ununiformity of granules increases with increase in amount of ethocel used and regular shape of microsphere showed in figure 2 and 3.

The formulations F2 released 72.3% as shown in figure 4, whereas the formulations F3 and F4 released 67.7% and 67.4% respectively at nine hour of *in vitro* drug release due to more viscous of syrup formulation.

CONCLUSION

Microspheres enriched syrup has been developed to provide oral delivery of ambroxol hydrochloride with taste masked. The microspheres showed sustained release of drug through syrup, indicating better potential of delivery system as compared with plain syrup of ambroxol hydrochloride. If this process can be scaled-up to manufacturing level; this technology has the potential to provide the oral ambroxol hydrochloride microspheres enriched syrup with better patient compliance. On the grounds of efficacy and improved patient compliance due to reduced frequency of application, microspheres enriched syrup formulations will have significantly better role in treatment of chronic bronchitis and management of cough.

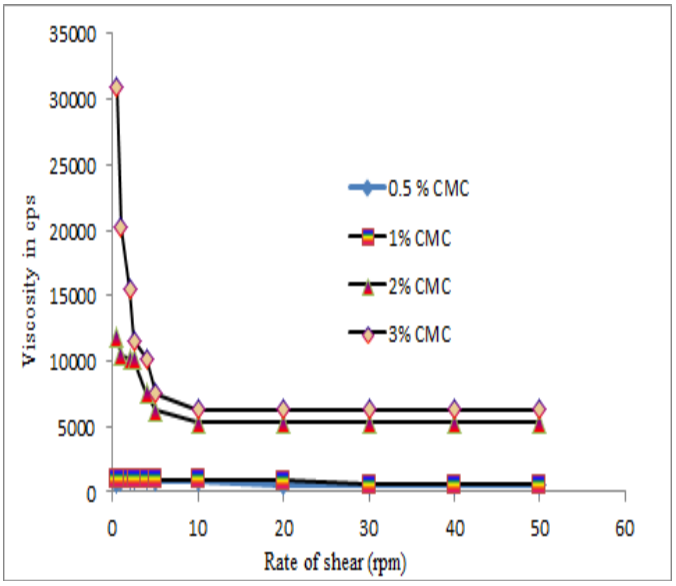

Figure 1. Showing the viscosity of profile of microspheres enriched syrup

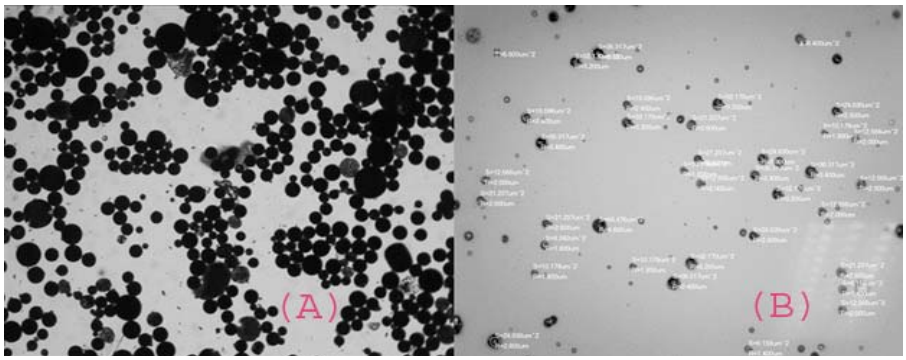

Figure 2: photograph A and B showing optical microscope view

Figure 3. SEM photography C showing the microsphere shape and photography D showing the appearance of microspheres enriched syrup

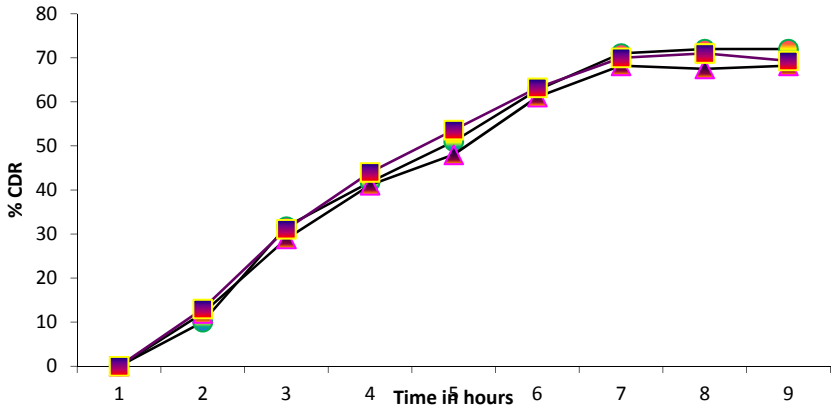

Figure 4. Showing the *in vitro* release of formulation

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