ORIGINAL ARTICLE

Formulation and Evaluation of Doxylamine Succinate Fast Dissolving Buccal Films

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Abstract

Aim: This study deals with the formulation of fast dissolving buccal films of doxylamine succinate is an antihistaminic commonly used for the prevention and treatment of nausea and vomiting in pregnancy. Doxylamine is a histamine H1 antagonist with pronounced sedative properties. It is used in allergies, antiemetic, and hypnotic. Doxylamine has also been administered in veterinary applications and was formerly used in Parkinsonism. The concept of fast-dissolving drug delivery emerged from the desire to provide the patient with a more conventional means of taking their medication. **Materials and Methods:** In the present research work, various trials were carried out using film forming agents such as maltodextrin, gum karaya, and xanthan gum to prepare an ideal film. Emulsion evaporation method was used for the preparation of films. **Results and Discussion:** The prepared films were evaluated for weight uniformity, drug content, film thickness, folding endurance, dispersion test, and curling. The *in vitro* dissolution studies were carried out using simulated salivary fluid (pH 6.8 phosphate buffers). About 98% of the drug was found to be released from the film prepared with the drug excipient interaction studies carried out by differential scanning calorimetry analysis and Fourier transform infrared studies, and the results revealed that there were no major interactions between the drugs and excipients used for the preparation of films.

Key words: Buccal films, emulsion evaporation method, gum karaya, maltodextrin, xanthan gum

INTRODUCTION

The oral cavity has been investigated as a site for drug delivery for a long period. Drug delivery through the oral cavity offers many advantages. Among all the routes of administration, the oral route is the most preferred route in the designing of dosage form than drug delivery design by other routes of administration.[1,2] The oral mucosa is conveniently and easily accessible and therefore allows uncomplicated application of various dosage forms. Furthermore, the oral mucosa is robust against local stress or damage and shows fast cellular recovery. Active substances can be administered locally to treat oral diseases such as periodontal disease, bacterial, and fungal infections. A systemic action can be achieved via drug permeation through the mucosal epithelium.[3,4] The concept of fast-dissolving drug delivery emerged from the desire to provide the patient with a more conventional means of taking their medication. Fast dissolving films recently have acquired great importance in the pharmaceutical industry due to their unique properties and specific advantages such as no need of water for disintegration, accurate dosing, rapid onset of action, ease of transportability, ease of handling, pleasant taste, and improved patient compliance.[5,6] Fast dissolving buccal film is a type of drug delivery system, which when placed in the oral cavity it rapidly disintegrates and dissolves to release the medication for oromucosal and intragastric absorption, without chewing and intake of water.[7,8] This technology evolved over the past few years from the confection and oral care markets in the form of breath strips and became a novel and widely accepted form by consumers. These films have the potential to deliver the drug systemically through the intragastric, sublingual or buccal route of administration and also have been used for local action.[9-11] Doxylamine is a histamine H1 antagonist with pronounced sedative properties. It is used in allergies,

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antiemetic, and hypnotic. Doxylamine has also been administered in veterinary applications and was formerly used in Parkinsonism. It is a combination of a pain reliever, a cough suppressant, and an antihistamine. It is used to treat the aches and pains, cough, fever, headache, runny nose, and sneezing of a cold. The half-life of zolmitriptan is 2-3 h and it undergoes hepatic metabolism, the absolute oral bioavailability is about 45%.[12] The present work was aimed to improve the bioavailability and efficacy doxylamine succinate by preparing rapidly dissolving buccal films.

MATERIALS AND METHODS

Doxylamine succinate was obtained as gift sample from Yarrow Chemicals, Hyderabad. Maltodextrin was obtained from Mylan Hyderabad. Xanthum gum and gum karaya were obtained from Yarrow Chem. Ltd., Mumbai. Cinnamon oil, mannitol, saccharin, starch, and citric acid were obtained from Qualigens Fine Chemicals., Mumbai. Polyethylene glycol (PEG) 6000 was obtained Sisco Research Laboratories Pvt., Ltd., Mumbai.

Preparation of doxylamine succinate buccal film

Doxylamine succinate buccal films were prepared by emulsion evaporation method. Cinnamon oil (oil phase) and Tween 80 were taken in a 50 ml beaker and mixed well using magnetic stirrer to get a clear solution which is labeled as Solution A. Solution B is prepared by taking sufficient quantities of PEG 6000 and starch in another beaker, sufficient amount of water was added and heated on heating mantle until a clear solution was obtained (aqueous phase). Film-forming polymers, sweetening agents, and citric acid were dissolved in distilled water to obtain Solution C. Solution B was carefully added to the Solution A with continuous stirring for 10 min to get a milky white emulsion. Then, the accurately weighed amount of drug was added to the emulsion and was stirred continuously for 10 min. Finally, the Solution C was added to the above and was stirred continuously for 1 h. The emulsion obtained was casted on the nonadhesive base plate and dried under infrared lamp for 24 h. After complete drying, the films were cut into required sizes. Various trials were carried out to optimize the formula for the preparation of doxylamine succinate films. The compositions of prepared films were given in Table 1.

Evaluation of physical parameters for doxylamine succinate buccal fast dissolving buccal films[13,14]

The film formulations were further evaluated for physical parameters. Thickness of the film was measured using screw gauge. Folding endurance of the film was determined by repeatedly folding a small strip of the film at one place. Air bubble entrapment is a common phenomenon that we see in all liquid formulations. The presence of air bubbles leads to improper drug content and content uniformity. Entrapment of air bubbles is completely absent in all formulations before casting the film and after drying the film. Curling of the films is observed normally in film formulations prepared using solvent casting method to minimize curling of film starch (1.6%) is used as anti-curling agent. The results of the physical evaluation test were given in Table 2.

In vitro dissolution studies

Dissolution studies were performed on all the film formulation using Franz diffusion cell apparatus containing simulated salivary fluid (pH 6.8 phosphate buffer) as a medium.[15] The dissolution studies were carried over a

Table 1: Composition of doxylamine succinate buccal fast dissolving films

Ingredients (%w/w)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Doxylamine succinate	1	1	1	1	1	1	1	1	1
Maltodextrin	30	30	30	30	30	30	30	30	30
Xanthan gum	20	30	40	-	-	-	-	-	-
Guar gum	-	-	-	20	30	40	-	-	-
Karaya gum	-	-	-	-	-	-	20	30	40
PEG 6000	20	20	20	20	20	20	20	20	20
Tween 80	18	18	18	18	18	18	18	18	18
Cinnamon oil	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Mannitol	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6
Sacharin	2	2	2	2	2	2	2	2	2
Sodium starch glyoclate	5	5	5	5	5	5	5	5	5
Starch	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6
Citric acid	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6

period of 15 min for all the formulations. Dissolution studies were carried out in triplicate, maintaining the sink conditions for all the formulations. A 5 ml aliquot of samples was withdrawn at regular time intervals, filtered and assayed spectrophotometrically at 262 nm. The drug release profiles for all the film formulations were shown in Figure 1.

Evaluation of various dissolution parameters

Dissolution parameters such as T_{50}, T_{90}, $DE_{5\%}$ first order rate constant, and Hixon-Crowell were calculated from the dissolution data obtained, and the results were given in Table 3.

Characterization

Based on the dissolution studies performed on all the formulations, the formulation F5 were further evaluated by Fourier transform infrared (FTIR), differential scanning calorimetry (DSC), and scanning electron microscopy (SEM) analysis.

FTIR spectroscopy

The FTIR spectra of doxylamine succinate maltodextrin, xanthan gum, and on optimized formulation F5 were obtained using Brucker FTIR spectrophotometer to study the interaction between drug and carrier in films. The samples were prepared in KBr discs (2 mg sample in 200 mg KBr) and the sampling range was 400-4000/cm and the resolution was 4/cm. The FTIR spectra were shown in Figures 2 and 3.

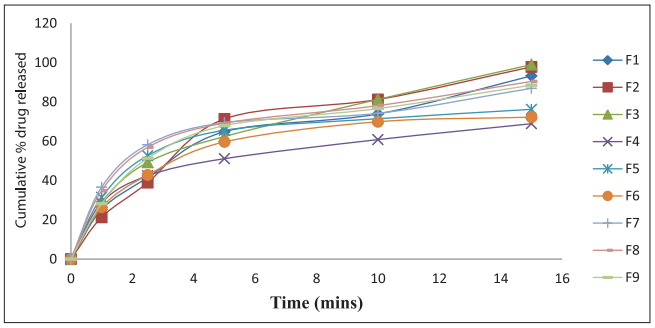

Figure 1: Drug release profiles for doxylamine succinate buccal fast dissolving buccal films

Table 2: Evaluation of physical parameters for doxylamine succinate buccal fast dissolving films

Formulation	Weight uniformity (mg)	Drug content (mg/film)	Film thickness (mm)	Dispersion test	Folding endurance (%)	Curling
F1	92	8.259	0.034	Passed	96	Absent
F2	90	9.543	0.034	Passed	99	Absent
F3	103	9.895	0.034	Passed	105	Absent
F4	65	7.5698	0.032	Passed	65	Absent
F5	68	8.2146	0.033	Passed	60	Absent
F6	70	8.5697	0.032	Passed	63	Absent
F7	103	7.963	0.034	Passed	81	Absent
F8	101	8.157	0.033	Passed	76	Absent
F9	97	8.367	0.034	Passed	71	Absent

Table 3: Evaluation of *in vitro* dissolution parameters for doxylamine succinate buccal fast dissolving films

Formulation	T_{50} (min)	T_{90} (min)	$DE_{5\%}$	First order		Hixon-Crowell	
				K (min^{-1})	R^2	K ($mg^{1/3}$/min)	R^2
F1	3.5	12.75	19.8	0.156	0.946	0.099	0.806
F2	3	12.25	19.6	0.234	0.954	0.1031	0.919
F3	2.5	14.75	22.8	0.267	0.904	0.076	0.932
F4	4.82	26.8	25.9	0.216	0.806	0.069	0.824
F5	3.6	23.2	36.8	0.211	0.87	0.071	0.763
F6	5.5	19.6	34.5	0.207	0.88	0.0806	0.751
F7	4.75	19.5	19.9	0.241	0.851	0.0752	0.921
F8	2.8	18.6	23.2	0.138	0.945	0.069	0.867
F9	3.8	20.6	25.6	0.188	0.937	0.0712	0.728

DSC

DSC measurements were performed on doxylamine succinate maltodextrin, xanthan gum and on optimized formulation F5 using DSC (Mettler-Toledo India Pvt., Ltd., Make DSC 1 with eSTAR software). The samples were placed in a sealed aluminum crucible and evaluated with a heating rate of 20°C/min at a temperature range of 20-2300°C. The thermograms were recorded and were shown in Figures 4-7.

SEM analysis

The SEM photographs were taken for the optimized film formulation F5 and doxylamine succinate pure drug. The SEM photographs were shown in Figures 8 and 9.

RESULTS AND DISCUSSION

In this study, doxylamine succinate is an antihistaminic commonly used for the prevention and treatment of Nausea and vomiting in pregnancy. Doxylamine is a histamine H1 antagonist with pronounced sedative properties. It is available as white color and is soluble in alcohol, water, and pH 6.8 phosphate buffer. Mean absolute oral bioavailability is approximately 25%. Based on the physicochemical and biopharmaceutical properties, this study was taken with

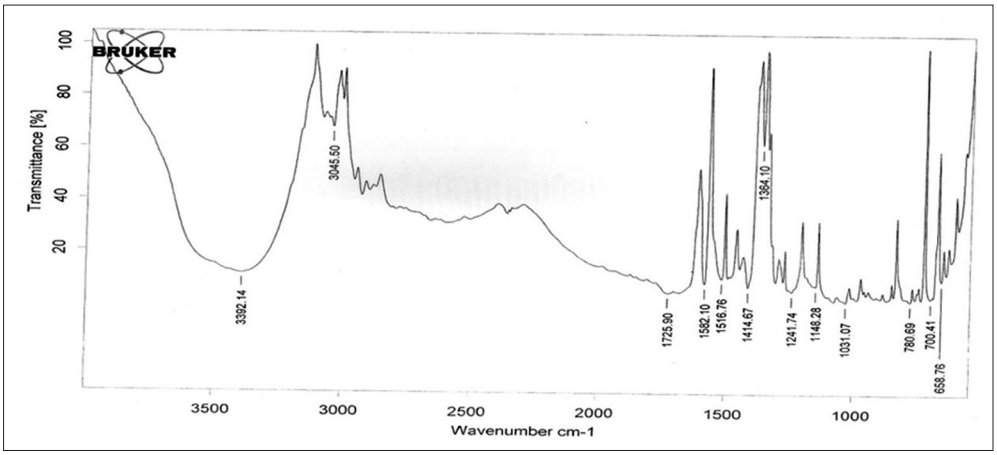

Figure 2: Fourier transform infrared spectrum of doxylamine succinate pure drug

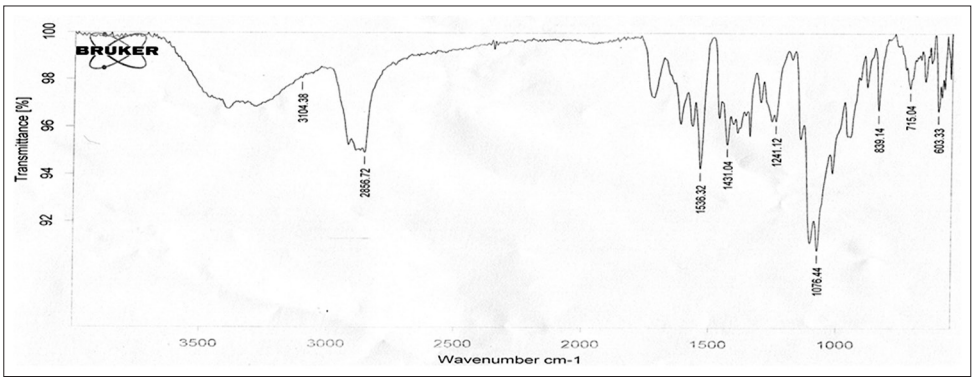

Figure 3: Fourier transform infrared spectrum of optimized film formulation F3

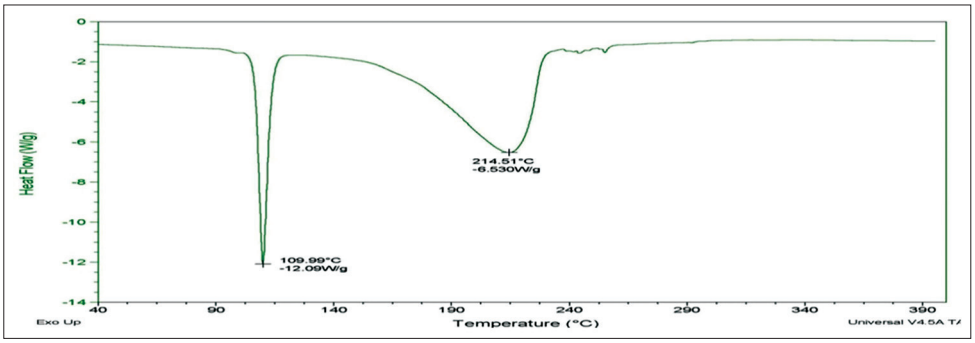

Figure 4: Differential scanning calorimetry thermogram of doxylamine succinate

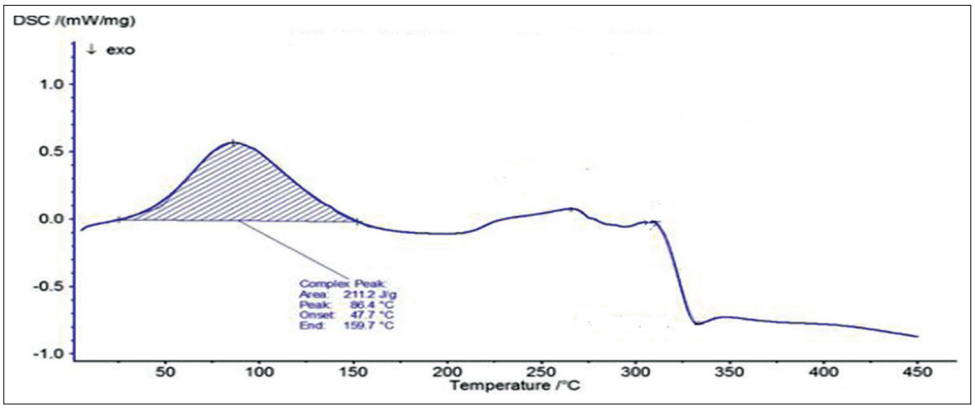

Figure 5: Differential scanning calorimetry thermogram of maltodextrin

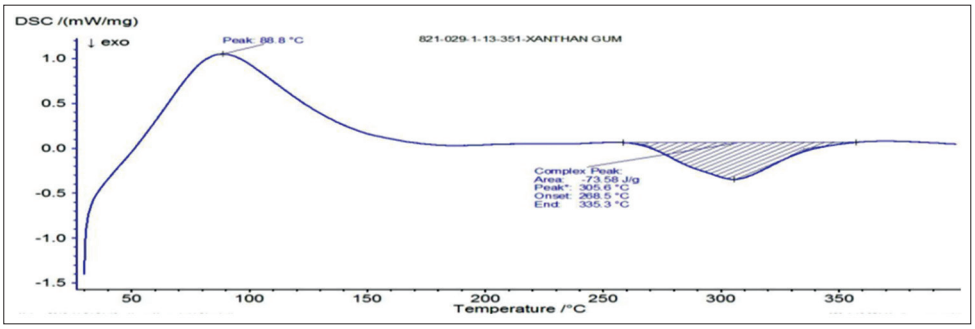

Figure 6: Differential scanning calorimetry thermogram of xanthan gum

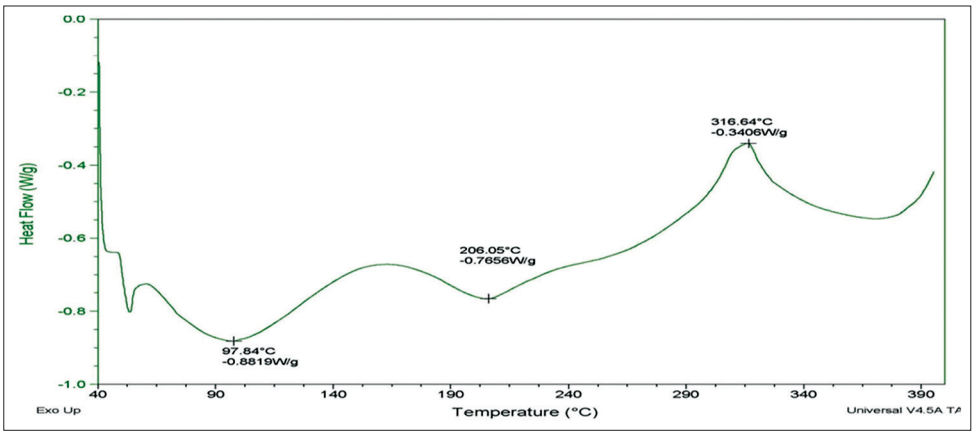

Figure 7: Differential scanning calorimetry thermogram of optimized film formulation (F3)

an aim to prepare fast dissolving films, using emulsion evaporation method, which offered a suitable and practical approach in serving desired objective of faster disintegration and dissolution characteristics with increased bioavailability. Maltodextrin, xanthan gum, and karaya gum were selected as the film forming agents, PEG 6000 as plasticizer, starch as anti-curling agent, and sodium starch glycolate as a super disintegrant. Moreover, the investigation mainly concentrated on optimizing PEG 6000 concentration and optimizing the best film forming agents. Drug and excipients used in the formulations were found to be compatible. No drug-excipient reactions were observed. 20% w/w concentration of plasticizer for the film formulation was elegant and did not break by applying pressure. Hence, optimum strength was obtained. Doxylamine succinate fast dissolving films were prepared by emulsion evaporation method. Emulsion evaporation method was suitable for drugs and polymers used. The thickness of all formulations was maintained at the range of 0.34 ± 0.03 mm. It is observed that formulation F3 showed good folding endurance compared with other films. Entrapment of air bubbles was completely absent in all formulations before casting the film and after drying the film. To minimize curling of film starch (1.6%) was used as an anti-curling agent. All the film formulations were found to be stable, and they were further evaluated for physical parameters such as weight uniformity, drug content, film thickness, dispersion test, folding endurance,

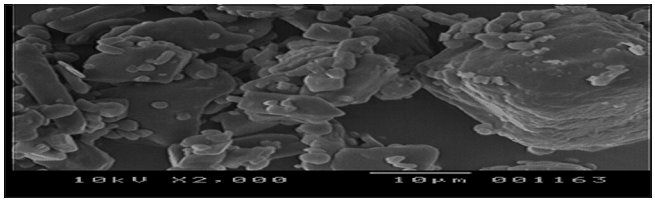

Figure 8: Scanning electron microscopy photograph of doxylamine succinate pure drug

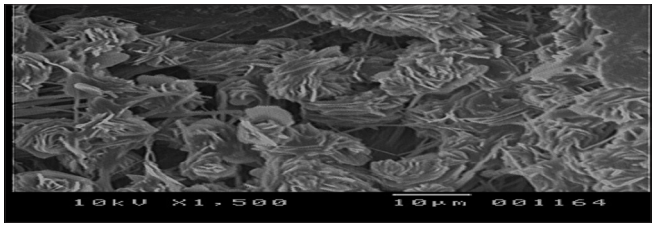

Figure 9: Scanning electron microscopy photograph of optimized film formulation (F3)

and curling. The average drug content of all formulations was measured as 10.0 ± 0.5 mg. The dispersion time for all the film formulations was <3 min. The compositions of doxylamine succinate buccal films were given in Table 1**.** The results of the evaluation of physical parameters for doxylamine succinate films were given in Table 2.

Dissolution studies were performed on all the film formulations using Franz diffusion cell apparatus containing simulated salivary fluid (pH 6.8 phosphate buffer) as a medium. The film formulations F1-F3 which were formulated using maltodextrin and xantham gum showed an average drug release of 90-99% within 15 min. The film formulations F4-F6, which were formulated using maltodextrin and Guar gum showed an average drug release of 60-80% within 15 min. The film formulations F7-F9 which were formulated using maltodextrin and karaya gum showed an average drug release of 70-90% within 15 min. Among all the film formulations the films that were prepared using xanthan gum, showed better drug release. The film formulation F3 prepared using xanthan gum showed 98.90% drug release in 15 min. The drug release profiles were showed in Figure 1. All the film formulations were found to be linear with first order release rate with R^2 values in the range of 0.97-0.98. Thus, the rates of drug release from all the film formulations were concentration dependent and were linear with the first order release rate constant (K_1). The Hixson-Crowell constants for all the film formulations were in the range of 0.0163-0.0509. $W_0^{1/3}$-$W_t^{1/3}$ versus time plots were found to be linear with R^2 values in the range of 0.96-0.97. Thus, the drug release from the film formulations was by diffusion of the drug from the polymeric matrix, followed by erosion of the polymer. The results of the *in vitro* dissolution parameters for doxylamine succinate films were given in Table 3.

The spectra of optimized film formulation F3 exhibited all the principle peaks present in the doxylamine succinate pure drug. Hence, there is no interaction between drug and polymers used in the formulation. The FTIR spectra were shown in Figures 2 and 3. The endothermic peak for the pure drug was obtained at 183.5°C, whereas for pure polymer maltodextrin at 86.4°C, respectively. The broad endothermic peak for the F3 film formulation was observed at 168.9°C The broad endothermic peak of the maltodextrin and drug may overlap, hence interaction between drug and polymer was studied using IR spectra only. The DSC thermograms were shown in Figures 4-7. The F3 formulation with the drug showed smooth, even surface in SEM analysis. The SEM images were shown in Figures 8 and 9.

The accelerated stability studies indicated that there were no visible and physical changes observed in the films after storage. It was also observed that there was no significant change in drug release from the films. The drug release characteristics of the films remained unaltered. Thus, the drug release characteristics of fast dissolving films designed were found to be quite stable.

CONCLUSION

Fast dissolving buccal films prepared in the study exhibited good film characteristic features as indicated by thickness measured, folding endurance, dispersion test, drug content, etc. The prepared films were found to be uniform, flexible, and 98% of the drug was released from F3 film formulation within 15 min that was desirable for fast absorption. Fast dissolving films of doxylamine succinate prepared by emulsion evaporation technique were found to be suitable for the prevention and treatment of nausea and vomiting in pregnancy.

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