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# Feasibility of xanthan gum–sodium alginate as a transdermal drug delivery system for domperidone

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**Abstract** The present investigation comprises the formulation and in vitro evaluation of domperidone loaded transdermal drug delivery system (TDDS) for controlled release. The polymer membranes were prepared using xanthan gum (XG) and sodium alginate (SA) by varying the blends compositions viz., 10:0, 8:2, 6:4, 5:5, 4:6, 2:8, and 0:10 (XG/SA, wt/wt, %). The drug loaded membranes were evaluated for thickness, content uniformity, tensile behaviours, and in vitro drug release studies. Domperidone was found to be compatible with the prepared formulation as revealed by Fourier transform infrared (FTIR) spectroscopy studies. In vitro release studies were carried out in open glass diffusion cell for a period of 8 h and it showed controlled release of drug from the XG/SA matrix. The present study concludes that, the prepared transdermal films can be used to achieve controlled release of drug and improved bioavailability.

## 1 Introduction

Controlled drug delivery by using polymers is one of the emerging technologies, which is generating significant interest because of therapeutic effectiveness of many drugs can be improved by combining them with polymers [1]. The conventional dosage forms of release pattern of drug at faster rate initially this leads to rise in blood level, for the peak and valley patterns of the drug levels in blood [2, 3]. The need to minimize blood level fluctuation of drug has lead to the development of controlled drug delivery system. Recently it is evident that the benefits of intravenous drug infusion can closely be duplicated by using skin as a port for drug administration, to provide continuous transdermal drug infusion in to systemic circulation. Among the various types of transdermal drug delivery systems available for different ailments, one of the major systems used is incorporation of drug in polymer matrix, which releases a drug in a controlled rate, constant administration of the drug, allowing continuous input of drugs with short biological half-life, but it also eliminates pulsed entry into the systemic circulation, which often cause undesirable side effects [4–7].

Transdermal applications, relative to other routes, are noninvasive, requiring the simple adhesion of a "patch" resulting in better patient compliance, improved bioavailability of a drug, and easy treatment termination. Therapeutically this dosage form provides constant plasma drug levels duplicating the benefits of intravenous infusion constantly. The present study envisages the use of xanthan gum and sodium alginate (XG/SA) blends as a carrier for TDDS. Domperidone is a freely soluble in water and is antihypertensive agent, non-peptide and exerts its action by blocked of angiogenesis II receptors. Domperidone has less half-life and low bioavailability, so it has been selected for the present study.

Xanthan gum (XG) is a naturally occurring white or yellowish white, free-flowing powder; soluble in both hot and cold water; practically insoluble in organic solvents. It is a high molecular weight polysaccharide gum it is produced by the pure fermentation of carbohydrate with *Xanthomonas campestris*. The percent composition of xanthan proposed for industrial use is as follows: glucose, 37; mannose, 43.4; glucuronic acid, 19.5; acetate, 4.5; and pyruvate, 4.4% [7, 8]. They are then purified by recovery

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with isopropyl alcohol, dried and milled [9, 10]. Xanthan gum is a hydrophilic polymer, which until recently had been limited use in thickening, suspending, and emulsifying water-based systems [11–13]. It appears to be gaining appreciation for the fabrication of pharmaceuticals as a suspending, stabilizing, and thickening agent with uniform drug release characteristics. Drug release property from XG matrices is preceded by polymer hydration, and processing variables that might affect its hydration would also affect its performance as a controlled release dosage form. Thus, the purpose of present investigation is to study processing variables at the laboratory and pilot scales that can affect hydration rates of xanthan. The rate of release from polymer carrier can be tailor-made by selecting a suitable polymer-blends composition and drug concentration. Sodium alginate (SA) is established as the most versatile polymer, used in a wide range of applications. The conventional used as excipient in drug products generally depends on the thickening, gel-forming, and stabilizing properties. Sodium alginate can play a significant role in the design of a controlled-release drug formulation [14, 15].

## 2 Experimental

### 2.1 Materials

Domperidone was obtained from M/s Mars Therapeutics and Chemicals, Secunderabad, India as a gift sample. It is a white, odorless crystalline powder, which is freely soluble in water, sparingly soluble in ethanol, and insoluble in chloroform and ether. It is dopamine antagonist with antiemetic properties. Plasma half-life of domperidone is 7–9 h with 15% oral bioavailability. Xanthan gum was procured from M/s Sigma Aldrich, USA. It is a white or yellowish white, free-flowing powder; soluble in both hot and cold water; practically insoluble in organic solvents. Sodium alginate was procured from Loba Chemie Pvt Ltd, Mumbai, India. It is a white to yellowish brown filamentous, grainy, granular or powdered forms of the sodium salt of alginic acid. It is used as gelling agent, emulsifier, stabilizer, and thickener to increase viscosity in food industry, also used in indigestion tablets and the preparation of dental impressions. Xanthan gum and Sodium alginate were used without further purification. Glycerol was obtained from Sd fine Chemicals, used as plasticizer, and all other chemicals were of analytical grade.

## 3 Preparation of XG/SA films with drug

The drug bearing films were prepared by using the solution casting method by using xanthan gum and sodium alginate in different composition. The SA and XG were dissolved in suitable solvent to get 2% w/v clear and homogenous polymeric solution. The specified amount of drug (10 mg/mm$^2$) was incorporated and the solution was stirred until all drugs get dissolved. Glycerin of 2% wt/wt was added as plasticizer. The prepared polymeric solution was poured on to cleaned petri dish and kept in a vacuum drier until to get the dried membrane. The cast polymer films with different formulations were then peeled off covered with aluminum foils and stored in a desiccator until further study.

### 3.1 Measurements

Mechanical properties, such as tensile strength and percentage elongation at break of XG/SA blends were measured as per ASTM D 638 using Universal Testing Machine (UTM) H 50KM, 50KN Hounsfield, UK. A minimum of three samples were tested for each formulation and the average value was recorded.

### 3.2 Content uniformity

In order to ascertain the uniform distribution of the drug in polymer membrane, the content uniformity test was performed. The wavelength of maximum absorbance ($\lambda_{max}$) of domperidone drug was determined by scanning a known concentration of a drug solution in the wavelength region 200–400 nm by using a Shimadzu 1601 UV/visible spectrophotometer. The $\lambda_{max}$ was found to be 277 nm. Specimen of 1 cm$^2$ was cut from the membrane in three different places and dissolved separately in 100 ml of normal saline by slightly warming. After cooling, the drug concentration of the polymer membrane was determined.

### 3.3 FTIR spectrophotometry

In order to evaluate the integrity and compatibility of the drug with the carrier polymer in the polymer–drug matrix formulations, IR spectra of the drug and its formulations were obtained by FTIR spectrophotometer using potassium bromide pellet method, Jasco-4100, Japan.

### 3.4 Drug diffusion studies

Drug diffusion studies were carried out in an open glass diffusion tube. A specimen dimension of 4 cm$^2$ was fixed to the hydrated cellophane membrane at one end of the open glass tube and placed in the receptor compartment containing buffer solution (normal saline). The assembly was placed on a magnetic stirrer and stirred at 100 rpm. The temperature of the system was maintained at 37 ± 1°C. A known amount of receptor medium (buffer) was withdrawn at regular intervals (for 8 h) and sink

condition was maintained by replacing equal volume of fresh saline. The drug concentration was determined by measuring the absorbance of the solution at 277 nm.

### 3.5 Higuchi plots

An attempt was made to ascertain whether the drug release confirm to the diffusion equation proposed by Higuchi which is given by:

$$f_1 = K_H\sqrt{t} \quad (1)$$

where, $f_1$ = amount of drug released, $K_H$ = Higuchi dissolution rate constant, and $\sqrt{t}$ = square root of time.

### 3.6 Peppas model fitting

The Koresmeyer–Peppas mathematical expression is used to evaluate the mechanism of drug release. The Koresmeyer–Peppas equation is as follows:

$$M_t/M_\infty = 1 - A(\exp^{-kt}) \quad (2)$$

$$\log(1 - M_t/M_\infty) = \log A - k_t/2.303 \quad (3)$$

where, $M_t/M_\infty$ is the fractional amount of drug released and $t$ is the time in hours. In this study, the release constant $k$ and constant $A$ were calculated from the slope and intercept of the plot of ln $(1 - M_t/M_\infty)$ versus time $t$.

### 3.7 Stability of the transdermal films

The stability of the drug incorporated polymer membrane was studied by placing the 4 $cm^2$ size specimens at 37 ± 1°C and at 75% RH for 6 weeks. The membranes were then evaluated for its content uniformity initially and at weekly intervals for 6 weeks.

## 4 Results and discussion

### 4.1 FTIR spectrophotometry

The FTIR spectra of domperidone and its formulations with polymer blends are shown in Fig. 1. The FTIR spectra of and its formulations were found to be identical. The characteristic IR absorption peaks of domperidone were observed at 1718 (C=O stretching), 1388 ($CH_2$ deformation), 1487 (C–N stretching), 3124 (O–H stretching), 2941 (N–H stretching), 696 (C–C stretching) and 2679 $cm^{-1}$ (C–H stretching). The FTIR spectra of the pure drug, as well as drug incorporated XG/SA formulations indicated that there is no chemical interaction occurred between the drug and the polymers used.

### 4.2 Mechanical properties

The measured mechanical properties, such as tensile strength and percentage elongation at break for the formulations are given in Table 1. From the table, it is observed that tensile strength decreased and percent elongation increased after incorporation of both xanthan gum and glycerol (plasticizer).

### 4.3 Stability studies

Stability studies of the formulations of domperidone loaded transdermal films were carried out to determine the effect of contents on the stability of the drug stability of the formulations were carried out at 25°C/60% RH, 30°C/65% RH and 40°C/75% RH for 90 days. There was no significant change in the drug content.

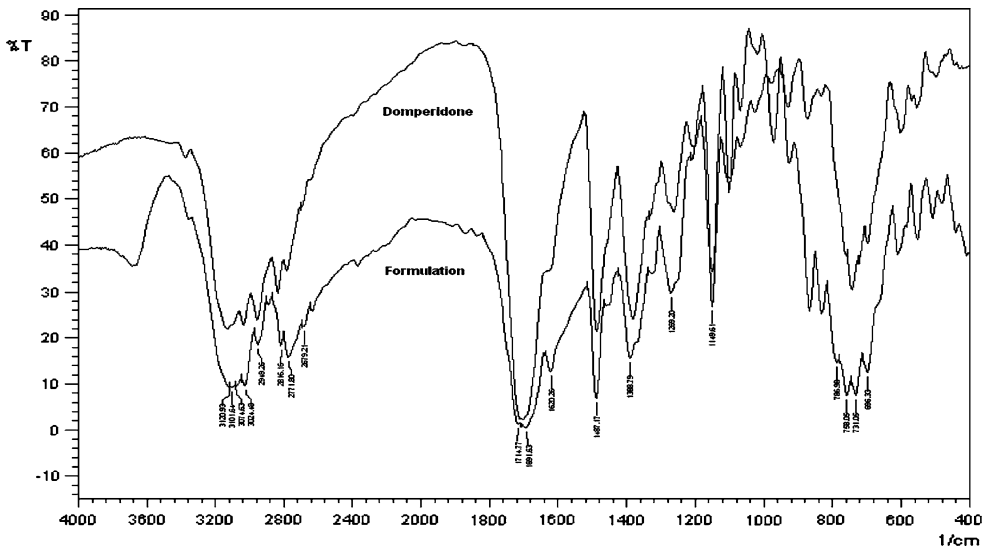


**Fig. 1** FTIR spectra of pure drug and optimized formulation

**Table 1** Mechanical properties and content uniformity data

| Formulation code | XG/SA | Tensile strength ($MPa/mm^2$) Mean ± SD* | Percentage elongation Mean ± SD* | Average thickness of film (μm) Mean ± SD* | Average film weight (mg) Mean ± SD* | Drug content (mg) Mean ± SD* |
|---|---|---|---|---|---|---|
| $F_1$ | 100/0 | 2.24 ± 0.011 | 38.22 ± 0.659 | 130 | 18.17 | 9.512 ± 0.014 |
| $F_2$ | 80/20 | 3.25 ± 0.014 | 35.36 ± 0.245 | 132 | 18.22 | 9.758 ± 0.256 |
| $F_3$ | 60/40 | 2.41 ± 0.023 | 29.54 ± 0.365 | 131 | 20.34 | 9.613 ± 0.186 |
| $F_4$ | 50/60 | 2.64 ± 0.024 | 24.01 ± 0.458 | 134 | 19.04 | 9.385 ± 0.014 |
| $F_5$ | 40/60 | 3.43 ± 0.152 | 19.49 ± 0.308 | 134 | 22.20 | 9.527 ± 0.014 |
| $F_6$ | 20/80 | 3.28 ± 0.120 | 21.65 ± 0.102 | 135 | 18.96 | 8.987 ± 0.311 |
| $F_7$ | 0/100 | 3.05 ± 0.035 | 30.35 ± 0.985 | 133 | 21.14 | 9.567 ± 0.212 |

* Mean ± SD, $n = 3$

**Table 2** Stability studies of formulation

| Sampling interval in days | Drug content (%) | | |
|---|---|---|---|
| | 25°C/60%RH | 30°C/65% RH | 40°C/75% RH |
| 15 | 98.902 ± 0.21 | 98.668 ± 0.26 | 98.059 ± 0.64 |
| 45 | 98.354 ± 0.24 | 98.184 ± 0.68 | 98.048 ± 0.51 |
| 60 | 97.802 ± 0.36 | 97.625 ± 0.24 | 97.105 ± 0.98 |

* Standard deviation, $n = 3$

### 4.4 Content uniformity

From Table 2, it was observed that the content uniformity value lies in the range 9.527–9.758 $mg/cm^2$. The results of content uniformity studies clearly indicate that the drug was uniformly distributed throughout the polymer membranes. These values are in the expected range as per Indian Pharmacopoeia (IP) standards (1–9 $mg/cm^2$).

### 4.5 Diffusion studies

Diffusion studies were carried out in an open glass diffusion tube, using hydrated cellophane as a diffusion membrane. Diffusion studies for all the films were carried out for 8 h in normal saline. Diffusion study of drug from the XG/SA membrane indicated that drug release from the formulation increases as the SA content increased. It was noticed that highest concentration of SA showed highest release of drug. In the first 2 h, there was a fast drug release indicated by a steep increase in the slope of the curve, this is due to the drug molecules present over the surface of the membranes which gets released. Later, a linear slow release of drug from the membrane was observed for the next 6 h (Figs. 2, 3, 4).

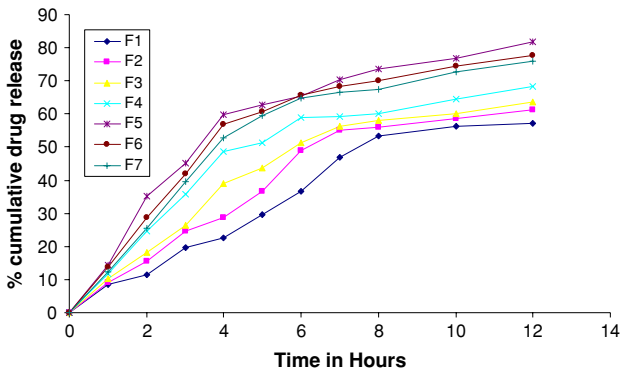


**Fig. 2** Release kinetic data of formulation $F_1$–$F_7$ cumulative (%) release of domperidone

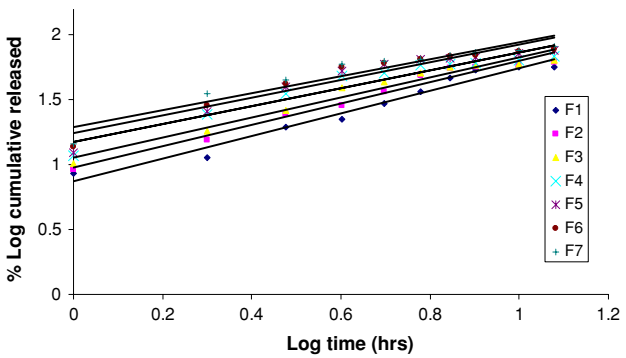


**Fig. 3** Release mechanism of all XG/SA-drug formulations

## 5 Higuchi plots

The amount of drug released as a function of square root of time was plotted. The plot should be linear if the drug release from the delivery system is diffusion controlled. The plots were linear and the results inferred that drug release from the transdermal drug delivery system was by diffusion.

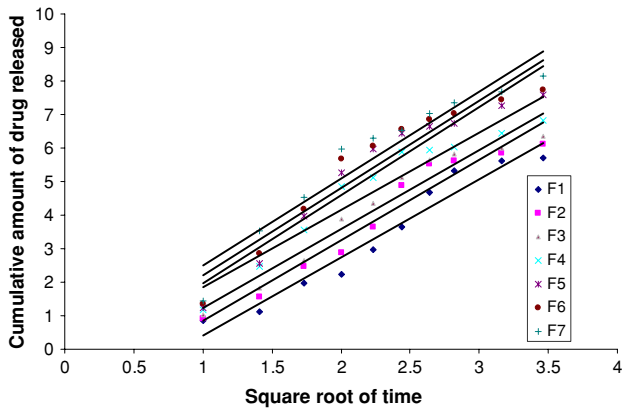


**Fig. 4** Higuchi plot for all XG/SA/drug formulation

### 5.1 Peppas model fitting

The data obtained from in vitro drug release studies was fit into Peppas model. From the plot of log $M_t/M_\infty$ versus time, the parameters such as release constant $k$, constant ($A$) and regression coefficient ($R^2$) were calculated. In all the cases the value of intercept $A$ were found to be more than 0.5. This indicates that the release of drug from all the formulations was found to be non-fickian release kinetics.

### 5.2 Stability studies

Stability studies of the domperidone loaded XG/SA transdermal films were carried out to determine the amount of drug content and also to determine the physical stability of the formulation. The stability studies were carried out at 25°C/60% RH, 30°C/65% RH and 40°C/75% RH for 90 days from the Table 2 it was noticed that there was no significant change in the drug content.

### 5.3 Conclusions

FTIR spectrograms of the domperidone incorporated XG films indicates that there is chemical interaction between drug and polymers used. From the content uniformity studies, it was found that the drug is uniformly distributed throughout the modified polymer membrane. From the tensile strength studies membranes have good property, Diffusion study indicated that the drug release from the formulation decreased as the concentration of XG increases. The release rate was found to follow first order rate kinetics and satisfies Higuchi's diffusion equation, which confirms that diffusion is one of the mechanisms of drug release. The result of stability studies carried out on optimized formulation showed that there was no significant change in drug content after 90 days, indicating that the prepared formulation is stable. The optimized formulation ($F_5$) showed maximum amount of drug release.

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