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Research Article

DESIGN AND EVALUATION OF TORSEMIDE CONTROLLED RELEASE MATRIX TABLETS

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ABSTRACT

Objective: The controlled release Torsemide matrix tablets were prepared using different natural polymers in various proportions as release retarding agents to control the torsemide release and to improve the patient compliance.

Methods: Torsemide matrix tablets were prepared by direct compression method. The matrix tablet is then evaluated for its thickness, hardness, friability, weight variation, drug content and *in vitro* release. The compatibility of drug excipients was reviewed using Fourier transform infrared (FTIR) and differential scanning calorimetry (DSC) studies.

Results: All the torsemide matrix formulations showed compliance with pharmacopoeial standards. Amongst all the formulations, formulation F9 containing pectin (10%) showed controlled drug release (99%) for 13 hrs, emerging as the best formulation. The formulation showed highest r^2 value of 0.9731 for zero order kinetics compared to first order kinetics indicating a drug release independent of concentration of the drug. Mechanism of drug release of optimized formulation F-9 showed non-Fickian diffusion. FTIR and DSC studies indicated no chemical interaction between the drug and polymer.

Conclusion: Hence, different natural polymers (guar gum, xanthan gum and pectin) in various proportions can be used to prepare matrix tablets of Torsemide having controlled therapeutic effect with improved patient compliance.

Keywords: Torsemide, Guar gum, Xanthan gum, Pectin, Controlled Release, Matrix Tablets.

INTRODUCTION

Conventional dosage forms are the most preferred and convenient option for drug delivery. However, it has poor patient compliance with ensuing undesirable toxicity and poor efficiency. A major challenge thus lies in optimizing the properties of the drug and its delivery mechanism in producing safe and efficient drugs. Consequently, there is a need for new drug delivery systems and they represent one of the frontier research areas [1,2]. An appropriately designed controlled drug delivery system can be a major advance concerning the targeting of drug to a specific organ or tissue and controlling the rate of drug delivery to the target site. A controlled release formulation that maintains an adequate and desired release of the drug over an extended period of time offers optimum biological response, prolonged efficacy, decreased toxicity and reduction in the drug plasma level fluctuation compared to conventional modes of delivery. Controlled drug delivery system dispenses the drug locally or systemically at a predestined rate for a specified period. Matrix tablets offer an effective means of oral controlled release formulation. They maintained therapeutic concentrations over prolonged periods and manufactured at a low cost.

Various types of polymers have been used as release rate modifiers to formulate matrix tablets. Over the years, Gums and Mucilage's are more oftenly used for the preparation of normal conventional dosage forms and also novel drug delivery systems. The use of polymers and other materials to prolong the drug release rate has become more popular. Natural polymers are better than the synthetic polymers because they are inert, non-toxic, low costand are also degradable in the body itself [3,4]. Natural polymers produce an appropriate drug release profile and are cost-effective. They have high gelling capacity and the drug releases when the polymer swells on contact with the aqueous medium. Drug releases through diffusion, dissolution and erosion mechanism [5].

Torsemide is a new generation loops diuretic belonging to pyridine sulfonylurea class and has been used for the treatment of both acute and chronic congestive heart failure, liver cirrhosis, and arterial hypertension. It exerts longer duration of action with a bioavailability of 80% and elimination half-life of 3-4 hrs compared with other loop diuretics [6-8]. Torsemide, when administered in an immediate-release formulation, exerted high rates of absorption and fluctuations in plasma concentrations resulting in poor patient compliance. Hence, the need for the design and evaluation of the controlled release formulation was critical. Torsemide controlled release tablets compared to immediate-release has similar systemic exposure, but significantly reduces the rate of absorption and fluctuations in plasma concentrations thus offering a better tolerability [9-11]. The aim of this study is to design controlled release tablets of Torsemide in a suitable polymer matrix thus enabling higher efficiency and better tolerability.

METHODS

Materials

Torsemide was a gift sample from Aurobindo Pharma, guar gum, xanthan gum was a gift sample from the Akhil Healthcare Private Limited, Pectin was a gift sample from Nikunj Chemicals, MCC PH 200 was a gift sample from FMC Biopolymer, Aerosil, Talc and Magnesium stearate was a gift sample from Cabot Sanmar Limited respectively. All other ingredients used were of analytical grade.

Methods

Matrix tablet preparation

Oral controlled release torsemide matrix tablets were prepared by direct compression technology. The investigated formulation compositions are shown in Table 1. All the powders passed through a 40 mesh sieve, and magnesium stearate passed through 60 mesh sieve. Mix the sifted torsemide, guar gum and micro crystalline cellulose pH200 for 15 minutes in an octagonal blender. Add sifted colloidal anhydrous silica and talc to the above mixture and blend it for 10 minutes. Magnesium stearate was finally added as a lubricant and blended for 5 minutes. The blend was directly compressed (7.5 mm diameter, round shaped, biconvex standard concave punches [D tooling]) using ten station rotary tablet punching

machine (Cad mach Machinery Ltd., Ahmedabad, India). Each tablet contained 20 mg of Torsemide. All the tablets were stored in airtight containers for further study.

Evaluation of tablets

Thickness

Ten randomly selected torsemide matrix tablets from each batch were used for thickness determination. Thickness of each tablet was measuredin mm using a digital Vernier Caliper (Mitutoyo Dial Thickness Gauge, Mitutoyo, Japan) and the results were expressed as mean values of 10 determinations with standard deviations.

Hardness

The hardness of ten randomly selected torsemide matrix tablets from each batch was measured using Pfizer Hardness tester (Secor Scientific Eng Corporation India) and expressed in kg/cm^2. Mean and standard deviation were calculated and reported.

Friability

Previously weighed tablets equivalent to 6.5 g from each batch were taken in Roche friabilator (Roche friabilator, Pharma labs, Ahmedabad, India). After 4 minutes (100 revolutions) of friabilator tablets were recovered. The matrix tablets were then made free from dust, and the total remaining weight of tablets was recorded. Friability was calculated from the following formula.

$$\text{Percentage friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Weight variation test

All prepared torsemide matrix tablets were evaluated for weight variation as per USP monograph. Twenty matrix tablets from each batch were weighed collectively and individually using an electronic balance. The average weight and percent variation of each matrix tablet was calculated. The percent deviation was calculated using the following formula [12].

Percentage weight variation = (Individual weight – Average weight/Average weight) ×100

Drug content

Ten matrix tablets were weighed and grounded in a mortar to get fine powder; powder equivalent to the mass of one matrix tablet extracted with pH6.8 phosphate buffer and filtered through 0.45 µ membrane filter paper. The torsemide content was determined spectrophotometrically at 263 nm using a UV- spectrophotometer (Elico, Ahmedabad, India) after suitable dilution [13].

***In vitro* release studies**

The *in-vitro* drug release studies were performed using a USP Type II dissolution apparatus. The dissolution medium was 900 ml of 6.8 pH phosphate buffer for 16 hrs. The temperature of dissolution medium was maintained at 37±0.5°C. The tablet was introduced into the medium, and then paddle lowered such that the lower end of the paddle was 25 mm above the base of the beaker which was set to rotate at 75 rpm. In all experiments, an aliquot of 5 ml sample of the leaching fluid was withdrawn at predetermined time intervals with a syringe fitted with a filter and replaced with an equal volume of drug-free dissolution fluid in order to maintain the sink condition. The samples were filtered and analyzed spectrophotometrically at 263 nm by using an Elico UV-visible double beam spectrophotometer [14].

Kinetic release profile

The torsemide release data from all the formulation were fitted in various kinetic models like zero order; first order Higuchi's model and Korsmeyer–peppas equations. A criterion for selecting the most appropriate model was based on goodness of fit, high regression coefficient value [15,16].

Fourier transform infrared (FTIR) studies and differential scanning calorimetry (DSC) studies

The pure Torsemide drug and formulations with guar gum, xanthan gum and pectin powders was mixed separately with IR grade KBr and pellets were prepared by applying a pressure of 10 tons in a hydraulic press. The pellets were analyzed in the frequency range between wave numbers 4000-400/cm at 4 cm^{-1} resolution [17,18].

Thermal properties of Torsemide and formulations with guar gum (F3), xanthan gum (F7) and pectin (F11) were evaluated by DSC. Indium/zinc standards were used to calibrate the temperature and enthalpy scale. Accurately weighed 3-6 mg samples were hermetically sealed in aluminium pans and heated at constant rate of 10°C/min over a temperature range of 40-240°C. Inert atmosphere was maintained by purging nitrogen gas at a flow rate of 25 ml/min [19]-[21].

RESULTS AND DISCUSSION

The physical attributes of the torsemide matrix tablet were found to be satisfactory. Physicochemical characterizations of different batches of Torsemide matrix tablets are given in (Table 2). The thickness of the matrix tablets was ranged between 3.40±0.08 mm and 3.74±0.08 mm. All the batches showed uniform thickness. Weight variations for different formulations were found to be 148±1.45 to 152.0±0.1mg. The average percentage deviation of all torsemide tablet formulations was found to be within the limit, and hence all torsemide formulations passed the test for uniformity of weight as per official requirement. The hardness of all the torsemide matrix tablet formulations was ranged from 6.0±0.44 to 7.5±0.55 kg/cm^2. The percentage friability of all the torsemide formulations was ranged from 0.23% to 0.65%. In the present study, the percentage friability for all formulations was within the prescribed limits. The percentage of drug content for F1 to F12 was found to be in between 97.25±0.85 and 101±0.03% of torsemide, which indicates that by direct compression, we can get a good quality of torsemide matrix tablets.

The torsemide release from the matrix tablets prepared using natural polymers was slow release up to 16 hrs, depending upon the

Table 1: Composition of torsemide matrix tablets

Formulations	Torsemide	Guar gum	Xanthan gum	Pectin	MCC 200	Aerosil	Talc	Magnesium stearate	Total weight (mg)
FT1	20	15	-	-	109.25	3	2	0.75	150
FT2	20	18.75		-	105.5	3	2	0.75	150
FT3	20	22.5	-	-	101.75	3	2	0.75	150
FT4	20	26.25	-	-	98	3	2	0.75	150
FT5	20	-	15	-	109.25	3	2	0.75	150
FT6	20	-	20	-	104.25	3	2	0.75	150
FT7	20	-	22.5	-	101.75	3	2	0.75	150
FT8	20	-	25	-	99.25	3	2	0.75	150
FT9	20	-	-	15	109.25	3	2	0.75	150
FT10	20	-	-	20	104.25	3	2	0.75	150
FT11	20	-	-	22.5	101.75	3	2	0.75	150
FT12	20	-	-	25	99.25	3	2	0.75	150

concentration and type of natural polymer used. The order of increasing release retarding effect observed with various natural polymers was pectin < xanthan gum < guar gum. The cumulative percent drug release was decreased by increasing natural polymer concentration. The comparative dissolution profile is presented in Fig. 1a-c.

Based on the results of all formulations, F9 was selected as best formulation because it showed 99% cumulative drug release at the end of 13 hrs. F9 formulations follow zero order release kinetics with a regression value of 0.973. Korsmeyer–Peppas plots, n=0.886 indicating that the torsemide release mechanism followed anomalous transport mechanism.

Kinetic parameters of matrix tablets

The *in vitro* dissolution data were fitted in different kinetic models *viz*. Zero order, the first order, Higuchi and Korsmeyer–Peppas equation (Table 3). The zero-order plots were found to be linear as indicated by their high regression values offormulations. The release exponent n was between 0.886 and 1.456, which appears to indicate anomalousand super Case II transport.

FTIR studies

FT-IR studies were carried out to know the compatibility. FT-IR results revealed that there was no significant difference in the peaks of torsemide and polymers in matrix tablets compared to pure torsemide as shown in Fig. 2. It was found that there was no interference to the torsemide with excipients and polymer used in the formulations.

DSC studies

DSC thermo grams of pure torsemide shows sharp endothermic peak at 164.81°C. Similar endothermic peaks were obtained at 168.67°C for the formulation prepared with guar gum (F3), at 166.68°C for the formulation prepared with xanthan gum (7), at 166.62°C for formulation prepared with pectin (F11). The presence of all peaks indicates that all ingredients are compatible with Torsemide and there is no incompatibility between the selected ingredients. Thermogram of different formulations and drug are shown in Fig. 3.

CONCLUSION

The present research was to study the effect of various natural polymers on *in vitro* release rate from sustained release tablet of torsemide. Different types of matrix forming polymers guar gum, xanthan gum and pectin were studied. Formulation F9 containing pectin 10% showed the drug release for 13 hrs, emerging as best formulation. The cumulative percentage Torsemide release was decreased withthe increase in natural polymer concentration. Mechanism of drug release of optimized formulation F9 found to be zero order non-Fickian diffusion. FTIR and DSC studies proved the no chemical interaction between torsemide and natural polymer of the developed matrix tablets. The controlled and efficient drug delivery system developed in the present study will maintain plasma torsemide levels better, which will overcome the drawbacks associated with the conventional therapy.

Table 2: Physicochemical properties of torsemide matrix tablets

Formulation code	Weight variation (mg)[b]	Thickness (mm)[a]	Tablet hardness (kg/cm^2)[a]	Friability (%)	Drug content (%)[a]
F1	150±0.33	3.70±0.060	6.0±0.44	0.63	98.12±1.2
F2	150±1.31	3.50±0.090	7.0±0.46	0.65	98.20±0.2
F3	150±1.31	3.60±0.080	6.5±0.43	0.33	98.50±0.2
F4	150±1.42	3.52±0.090	7.0±0.54	0.45	98.48±0.62
F5	151.0±1.45	3.74±0.08	6.0±0.56	0.23	98.5±0.96
F6	151.0±1.33	3.60±0.09	7.5±0.05	0.25	97.25±0.85
F7	151.0±1.03	3.70±0.09	6.8±0.05	0.31	97.55±0.85
F8	152.0±0.1	3.64±0.09	7.2±0.43	0.35	99.8±0.08
F9	150.0±1.35	3.50±0.05	7.0±0.5	0.45	99.1±0.05
F10	149.0±1.39	3.40±0.08	7.2±0.16	0.56	98.2±0.09
F11	150±1.45	3.54±0.08	6.8±0.16	0.55	99.4±0.05
F12	148±1.45	3.45±0.08	7.1±0.51	0.49	101±0.03

Mean±SD; (a) n=10, (b) n=20, SD: Standard deviation

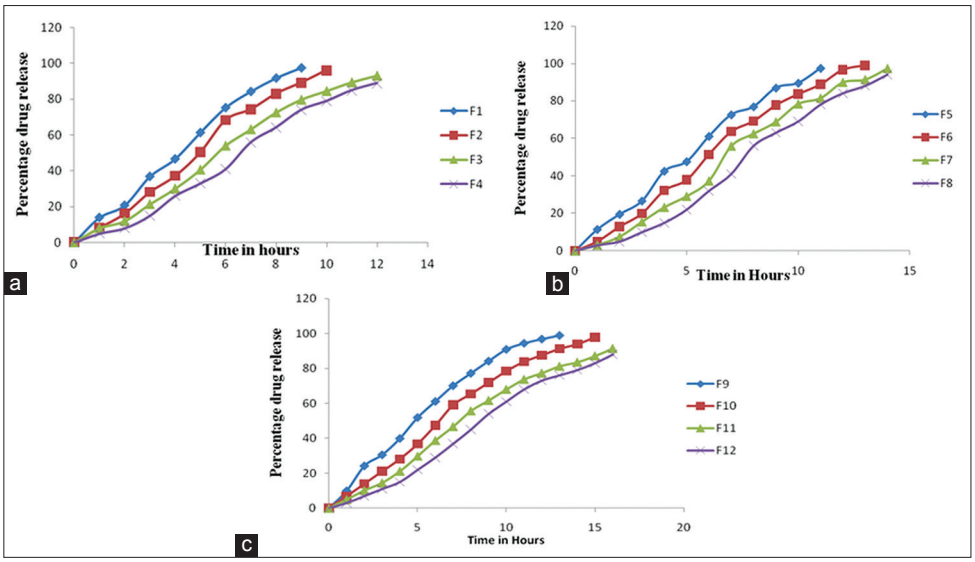

Fig. 1: (a) Comparative release profile of formulation F1 to F4, (b) comparative release profile of formulation F5 to F8, (c) comparative release profile of formulation F9 to F12

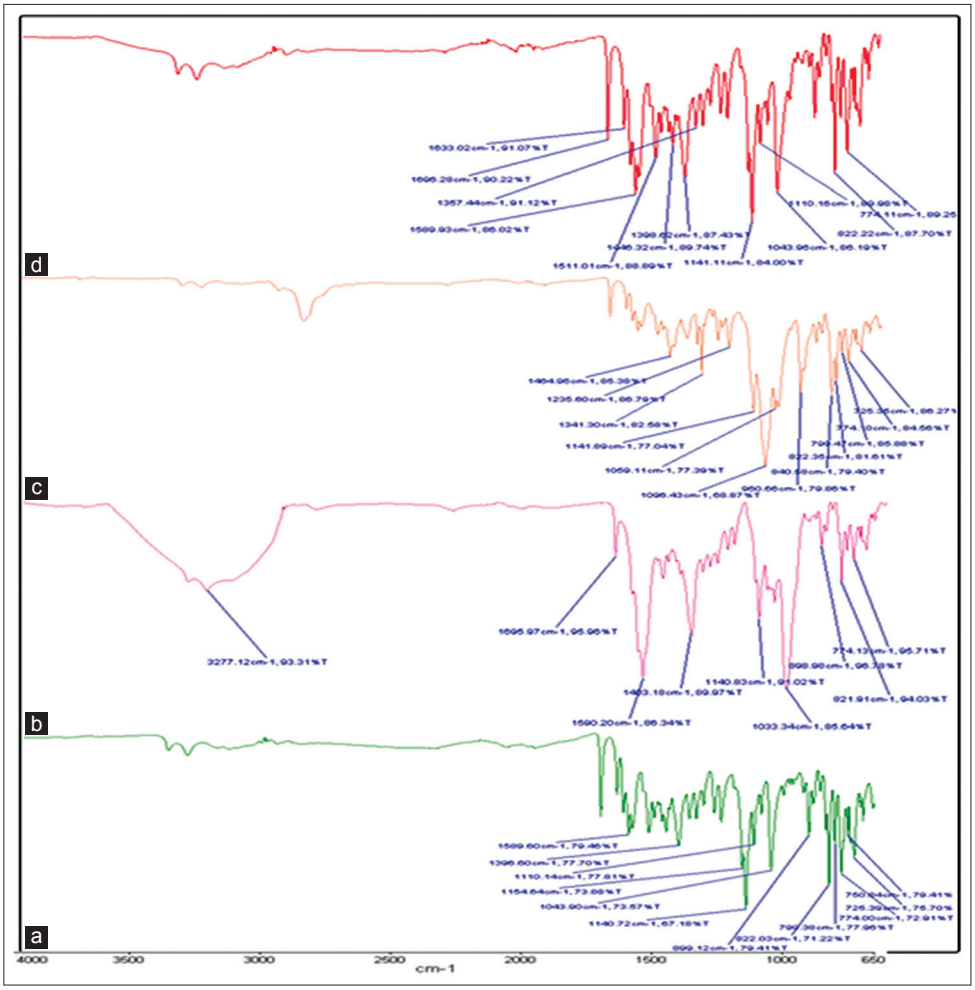

Fig. 2: Fourier transform infrared spectra of (a) torsemide pure drug, (b) formulation F3, (c) formulation F7, (d) formulation F11

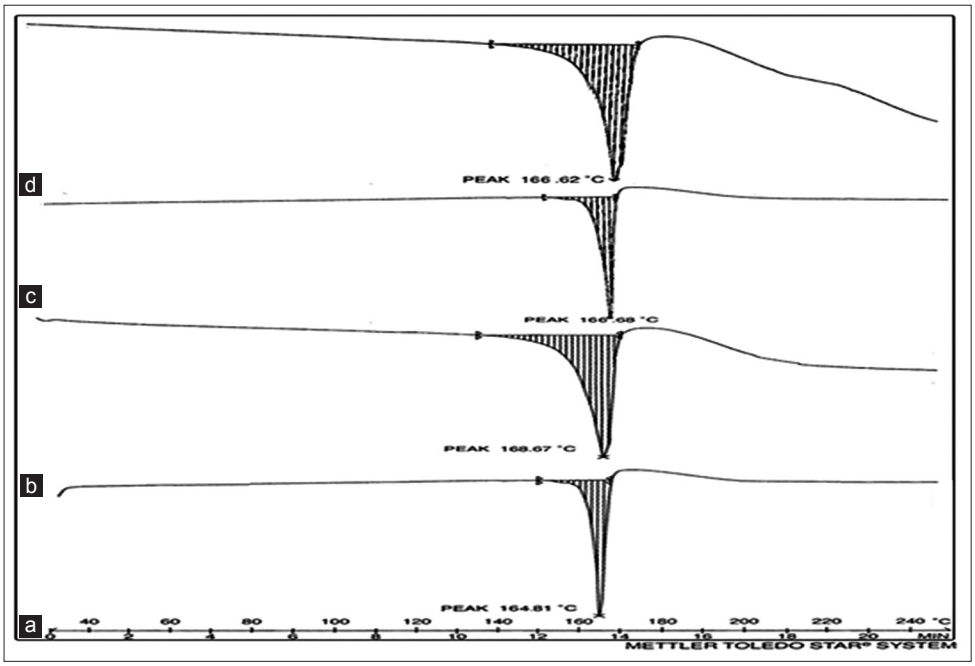

Fig. 3: Differential scanning calorimetry thermo gram of (a) torsemide pure drug, (b) formulation F3, (c) formulation F7, (d) Formulation F11

Table 3: Kinetic parameters of matrix tablets

Formulation code	F1	F2	F3	F4	F5	F6
Zero order (r^2)	0.9773	0.9892	0.9625	0.9896	0.9645	0.9651
First order (r^2)	0.8466	0.8783	0.9197	0.9432	0.9857	0.9766
Higuchi (r^2)	0.9871	0.9863	0.9845	0.9121	0.9709	0.9877
Peppas (r^2)	0.986	0.993	0.991	0.985	0.9910	0.9900
Peppas (n)	0.952	1.111	1.144	1.269	0.9350	1.1720
Formulation code	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
Zero order (r^2)	0.9421	0.9621	0.9731	0.9671	0.9656	0.9725
First order (r^2)	0.9751	0.9451	0.9604	0.9067	0.9541	0.9678
Higuchi (r^2)	0.9791	0.9791	0.9751	0.9791	0.9722	0.9897
Peppas (r^2)	0.9910	0.9850	0.9850	0.9940	0.9930	0.9950
Peppas (n)	1.3590	1.456	0.8860	1.0430	1.1470	1.3180

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