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Preparation and Evaluation of Solid Dispersions of Modified Gum Karaya and Aceclofenac: Controlled Release Application

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ABSTRACT

The objective of the present investigation was to develop matrix solid dispersion (SD) of aceclofenac sodium with modified gum karaya (MGK) in the drug carrier ratio of 1:1, 1:2, 1:4, 1:8 and 1: 10 (SD₁ to SD₁₀) and to study its functionality as a matrix forming agent for oral controlled release formulations. MGK was characterized and compared with GK through swelling index, water retention capacity and ATRFTIR. MGK showed comparable swelling index and water retention capacity to GK. The prepared solid dispersions were characterized for their ATRFTIR, drug content, and in vitro release studies followed by various release kinetics and mechanism of release. The drug release profile showed concentration dependent release retardant potential of natural polymer from 99.91 to 72.29 % (SD₁ to SD₁₀). Kinetic profile showed good linearity with zero order i.e. exhibiting concentration independent release of drug and Hixson Crowell cube root law ($r^2 = 0.848$ to 0.925) demonstrating that the drug release from the SD was erosion based. Korsmeyer pepas model provide n values of 0.566 to 0.788 suggestive of release mechanism was non-Fickian or anomalous release (0.45 < n < 0.89), which point towards drug release follows both diffusion and erosion mechanism. The drug content was found to be between 99.39 % and 100.83% representative of drug uniformity in various formulation batches.

Keywords: modified gum karaya, matrix solid dispersion, release mechanism.

INTRODUCTION

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects. Oral controlled release dosage forms are the most common type of dosage forms offering numerous advantages compared to conventional dosage forms including improved efficiency, reduced toxicity, and improved patient compliance [1]. Controlled release is usually accomplished employing a membrane or matrix. Compressed polymeric matrices are commonly used as oral drug delivery systems and being increasingly investigated for controlled-release applications. They are usually easy and economical to

formulate [2]. Solid dispersion technique viz. solvent evaporation method has been used for the preparation of sustained release formulation. The use of natural polymers for pharmaceutical applications is smart because they are economical, readily available, non-toxic, capable of chemical modifications, potentially biodegradable and biocompatible. In addition that plant resources are renewable and provide raw material regularly [3]. Gum karaya (GK) is a natural gum exudate of *Sterculia urens*, belonging to the family 'Sterculiaceae'[4]. The tree is native to India and widely used in food industry, as additive. [5]. Aceclofenac, 2-[2-[2-[(2, 6dichlorophenyl) amino] phenyl] acetyl] oxy]-acetic acid, is a potent non-steroidal antiinflammatory drug, which is a commonly prescribed drug for the treatment of patients suffering with pain, rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. Aceclofenac directly blocks PGE2 secretion at the site of inflammation by inhibiting IL-Beta and TNF in the inflammatory cells. Aceclofenac sodium is newer derivative of diclofenac and having less GIT complication. It is rapidly and completely absorbed after oral administration, peak plasma concentrations reached within 1 to 3 hrs after oral dose. The plasma elimination half-life of the drug is approximately 4h, and dosing frequency of 2 times daily with dose of 100mg [6, 7]. To reduce the frequency of administration and improve patient compliance, Aceclofenac sodium is suitable candidate for making sustain release solid dispersion. The pharmacokinetics and dosage schedule supports once daily sustained release formulations for aceclofenac sodium for better control of pain, enhance clinical efficacy and patient compliance. Present investigation was aimed at exploring release retardant potential of MGK by formulating controlled release solid dispersion using highly water soluble drug. Previously it is explored as dissolution enhancer [8] and disintegrant [9].

MATERIALS AND METHODS

Material

Aceclofenac sodium and gum karaya were received as gift samples from /nayan Pharamceuticals, Patiala, India and lucid colloids limited, Mumbai, India respectively. Ethanol was procured from Production Operators Mississauga, Brampton, Ontario, Canada . All other reagents were used of analytical grade.

Preparation of MGK

The powder gum karaya is sieved through mesh no. 80. Preparation of MGK was done by the method reported by Murali Mohan Babu et al. (2000). Powder gum was taken in a porcelain bowl and subjected to heating at 120 °C for 2 h to prepare modified form of GK. The prepared modified form of GK was sieved # 80 mesh and stored in desiccators until further use [6].

Characterization of MGK

Swelling and water retention capacity

The study was carried out using a 100 ml stoppered graduated cylinder. About 1.0 g of GK powder was accurately weighed and transferred to a 100 ml graduate measuring cylinder. The initial volume of the powder in the cylinder was noted. The volume was made up to 100-ml mark with distilled water. The cylinder was stoppered and was shaken gently and set aside for 24 h. The volume occupied by the gum sediment was noted after 24 h. Swelling capacity of GK/MGK was expressed in terms of swelling index as follows. Swelling index (SI) was expressed as a percentage and calculated according to the following equation:

$$SI = \frac{V_t - V_o}{V_o} \times 100$$

Where, V_0 is the initial height of the powder in graduated cylinder and V_t denotes the height occupied by swollen gum after 24 hrs.

The contents from the measuring cylinder from the above test were filtered through a muslin cloth and the water was allowed to drain completely into a dry 100 ml graduated cylinder. The volume of water collected was noted and the difference between the original volume of the mucilage and the volume drained was taken as water retained by the sample referred as water retention capacity or water absorption capacity of the polymer.

Preparation of solid dispersion of drug

Solid dispersions of aceclofenac prepared with MGK in 1:1, 1:2, 1:4, 1:8 and 1:10 w/w (aceclofenac: MGK) are represented as SD_1 , SD_2 , SD_4 , SD_8 and SD_{10} , respectively. Solvent evaporation method was used to prepare solid dispersions of aceclofenac in MGK. Solution of aceclofenac (200 mg) in 70% v/v ethanol (25 ml) was prepared, to which appropriate amount of MGK was added in rota evaporator flask. Under reduced pressure at 40 °C solvent was evaporated. Then the resulting residue dried under vacuum for 2 h, then scratched with the help of spatula and was stored overnight in a desiccator. The mass obtained then crushed, pulverized and sieved through a mesh no. 80.

Evaluation of solid dispersion

ATRFTIR: An IR spectrum of the sample was recorded as to ascertain the presence of different groups. ATR of drug, GK, MGK and solid dispersion batches was recorded. The scanning range was kept in between 500-3500 cm⁻¹.

Estimation of drug content

The formulation equivalent to 50 mg of aceclofenac sodium was weighed and dissolved in 100ml volumetric flask. The resulting solution was filtered and diluted suitably with distilled water. The absorbance was measured at 272 nm with a UV-Vis double-beam spectrophotometer (Systronics 2202, India) and the amount of drug in each formulation was calculated.

In vitro dissolution

The release of aceclofenac from the solid dispersion systems was measured by eight stage dissolution apparatus II (paddle) USP (Lab India, DS 8000). The test was performed in $37\pm 0.5^{\circ}$ C with a rotation speed of 50 rpm using 900 ml of buffer (pH 6.8) as a dissolution medium. According to the sampling plan, samples of 5 ml were withdrawn and immediately replaced with an equal volume of the respective dissolution medium maintained at $37\pm 0.5^{\circ}$ C. Test samples were filtered through Whatman filter paper No. 41 (Whatman Paper Limited, UK) and assayed for aceclofenac at 272 nm using a blank solution as reference with a UV-Vis double-beam spectrophotometer (Systronics 2202, India). The tests were performed in triplicate.

Release kinetic

To study the release kinetics, the data obtained from *in vitro* drug release studies were plotted in various kinetic models.

Zero order, as cumulative amount of drug released vs. time (Figure 3), describes concentration independent drug release rate from the formulation (Equation 1)

 $C = k_0 t$

(1)

Where k_o is the zero-order rate constant expressed in units of concentration/time and t is the time in hours.

First order, as log cumulative percent drug remaining vs. time (Figure 4), describes concentration dependent drug release from the system. (Equation 2)

$$LogC = LogC_0 - kt/2.303$$
 (2)

Where C_0 is the initial concentration of drug and k is the first order constant

Higuchi's model [10], as cumulative percentage of drug released vs. square root of time (Figure 5), described the release of drug based on Fickian diffusion as a square root of time dependent process from swellable insoluble matrix. (Equation 3)

$$Q = kt^{1/2}$$
(3)

Where k is the constant reflecting the design variables of the system

Hixson-Crowell cube root law [11], as the cube root of percentage drug remaining vs. time (Figure 6), correlated the release from systems with polymer erosion/dissolution resulting in a change in surface area and diameter of particles or tablets. (Equation 4)

$$Q_0^{1/3} - Q_t^{1/3} = k_{\rm HC} t \tag{4}$$

Where Q_t is the amount of drug released in time t, Q_0 is the initial amount of the drug in the tablets, and k_{HC} is the rate constant for the Hixson-Crowell rate equation,

Mechanism of drug release

Korsmeyer et al. [12, 13], as log cummulative % drug release vs. log time (Figure 7), derived a simple relationship which described drug release from a polymeric system (Equation 5). To find out the mechanism of drug release, first 60% drug release data was fitted in Korsmeyer–Peppas model:

$$M_t / M_\infty = k_{KP} t^n \tag{5}$$

Where M_t / M_∞ is fraction of drug released at time t, k_{KP} is the rate constant and n is the release exponent. The n value is used to characterize different release mechanisms as given in table for cylindrical shaped matrices.

Stability studies

The optimized formulation was packed in secured pack subjected to stability at room temperature in desiccators, to protect from moisture, for period of six months. The samples were withdrawn at 0, 3 and 6 months analyzed for drug content and drug release profile.

RESULTS AND DISSCUSION

Swelling Index and water retention capacity of the GK and MGK is almost comparable (table 1). The compatibility of drug to polymer was investigated by IR spectroscopy. The IR spectra of solid dispersion were compared with pure drug. No significant changes were observed in IR

spectra of GK and MGK (fig. 1). No considerable changes were observed in drug peaks in solid dispersion batch indicating absence of any interaction (fig. 2). Drug content of the solid dispersions was found to be between 98.52 % and 100.83% shown in table 2. All the solid dispersions showed the presence of high drug content and good uniformity of method employed for preparation. It indicates that the drug is uniformly dispersed in the powder formulation. Therefore, the method used in this study appears to be reproducible for preparation of solid dispersion. *In vitro* drug release profile gives us an idea about release retardant potential of MGK. Drug release is also influenced by drug polymer ration with increase in polymer ratio from 1 to 8, the drug release from 99.91 to 73.69 % (SD₁ to SD₈) shown in fig. 3.

This release retardant property may be due the matrix formation of the polymer and enclosing the drug in matrix commencing slow release of drug either through diffusion or erosion of polymer. Further increasing in polymer concentration does not affect significantly the release as evidenced by 72.29% (in case of SD_{10}), which suggest that the sufficient polymer is available for matrix formation, additional increase in polymer does not affect the release. In order to study the exact release kinetic of drug from SD, drug release data was analyzed according to zero order, first order, Higuchi square root, and Hixson Crowell cube root law (table 3).

The regression coefficients (table 3) obtained for zero order kinetics were found to be higher (R^2 = 0.977 to 0.998) when compared with those of first order kinetics (R^2 = 0.794 to 0.883), indicating that drug release independent of concentration from all formulation. All the formulation batches showed good linearity with Hixson Crowell cube root law (r^2 = 0.848 to 0.925) signifying that the drug release from the SD was erosion based means decrease in surface area and diameter of particles with polymer erosion. To categorize the mechanism of drug release, in vitro information was en suite in korsmeyer-pepas model (table 3). All the formulation shows good linearity (R^2 = 0.988 to 0.996), with the slope (*n*) values 0.566 to 0.788, indicating that release mechanism was anomalous non-Fickian or anomalous release (0.45 < *n* < 0.89). Based on swelling and erosion studies, it was concluded that SD undergo swelling based diffusion as well as erosion during the dissolution study, which indicates that polymer relaxation had a role in drug release mechanism.

However, it can be over and done with that release kinetics was found to be diffusion coupled with erosion. Effect of real time storage conditions on the drug condition and *in vitro* of various batches of solid dispersion were shown in table 4. Stability data clearly indicate that storage condition has no effect on drug content and *in vitro* dissolution data showing that prepared formulations were stable.

Products	Swelling index	Water retention capacity (ml)
GK	34.5 ± 3.78	40.14 ± 2.52
MGK	33.8 ± 2.92	39.52± 2.89

Table 1. Characterization of gum karaya and modified gum karaya

Batch	Drug Content (%)
SD_1	99.78
SD_2	99.52
${ m SD}_4$	99.39
SD_8	100.83
SD_{10}	100.12

Table 2. Drug content analysis of various batches

Table 3. Release kinetic and mechanism of drug release

Batch	Zero	order	First order		Higuchi		Korsmeyer- Peppas			Hixson- Crowell	
	r^2	$k_0(h^{-1})$	r^2	$k_1(h^{-1})$	r^2	$k_{\rm H}({\rm h}^{1/2})$	r^2	n	$k_{KP}(h^{-n})$	r^2	$k_{KP}(h^{-n})$
SD ₁	0.977	0.134	0.883	-0.002	0.877	45.04	0.994	0.566	0.355	0.925	-0.005
SD ₂	0.991	0.127	0.833	-0.002	0.841	41.62	0.996	0.569	0.285	0.886	-0.004
SD_4	0.998	0.119	0.794	-0.001	0.794	37.50	0.988	0.608	0.099	0.848	-0.004
SD_8	0.985	0.103	0.842	-0.002	0.803	32.82	0.995	0.737	-0.279	0.877	-0.004
SD_{10}	0.996	0.102	0.837	-0.002	0.800	32.45	0.996	0.788	-0.417	0/878	-0.004

Table 4. Stability studies demonstrating data of various batches of solid dispersion

Batch	Parameter (months)								
]	Drug content (%	b)	In vitro dissolution (%)					
	0	3	6	0	3	6			
SD_1	99.78 ± 0.23	99.80 ± 0.70	99.76± 0.54	99.91±0.45	99.70±0.33	99.19±0.56			
SD_2	99.52 ± 0.11	99.50 ± 0.62	$99.47{\pm}0.52$	95.90±0.78	96.56±0.65	$95.30{\pm}0.49$			
SD_4	99.39 ± 0.67	$99.45{\pm}0.32$	99.42 ± 0.31	88.78±0.56	87.34±0.89	87.82±0.92			
SD_8	100.83±0.34	100.7 ± 0.50	100.8 ± 0.43	73.69±0.56	74.45±0.67	73.69±0.43			
SD_{10}	100.12±0.32	100.07 ± 0.21	100.1±0.37	72.29±0.91	73.90±0.78	72.29±0.91			



Figure 1. ATRFTIR spectra of GK (upper) and MGK (lower)



Figure 2. ATRFTIR spectra of drug (upper) , SD_8 (between) and SD_{10} (lower)



Figure 3: Zero order release model of aceclofenac from various solid dispersions



Figure 4. First order release model of aceclofenac from various solid dispersions



Figure 5. Higuchi release model of aceclofenac from various solid dispersions



Figure 6. Hixson-Crowell cube root plots of aceclofenac from various solid dispersions



Figure 7. Korsmeyer-Peppas model for mechanism of drug release

CONCLUSION

The research finding on solid dispersion using modified gum karaya clearly indicates towards its matrix forming and release retardant potential. Natural materials can be extensively used in the field of drug delivery because they are readily available, cost effective, eco-friendly, biodegradable and biocompatible due to their natural origin. It can be concluded that modified gum karaya can be used as matrix forming agent and release retardant for its pharmaceutical applications.

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