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Research Article

Gum Karaya: A release modifier employed in the formulation of matrix granules containing Amoxicillin trihydrate as a model drug

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ABSTRACT

Hydrophilic swellable polymers are widely used to control the release of drugs from matrix formulations. The natural polymers are biodegradable and nontoxic, which hydrate and swell on contact with aqueous media. The present investigation is aimed to formulate the controlled release matrix granules of Amoxicillin trihydrate with different concentration of a plant derived gum, gum karaya, using no other varying parameter. Prepared granules were evaluated for different micrometrics properties like bulk density, tapped density, Hausner's ratio, Carr's index. The drug content and swelling behaviour were also investigated along with drug release kinetics. Percent swelling of the granules was 10-107.87 % in phosphate buffer pH-6.8. The drug release data from the granules were fitted in kinetic models of zero order, first order and Higuchi. The granules with 10-15% of gum karaya reveal the dominance of the highly swollen layer which controls the drug release from the granules. The findings lead to the conclusion that the matrix granules can be compressed to tablet to get a successful oral controlled release formulation.

Keywords: Gum Karaya; Amoxicillin Trihydrate; Matrix Granules; Drug Release Kinetics

INTRODUCTION

In recent years the basic objective in the designing of dosage form is to reduce the frequency of dosing by modifying the rate of drug release kinetics as well as drug absorption. Regular research is going on in field of use of natural occurring biocompatible polymeric material in designing of dosage form for oral controlled release administration. In addition, controlled delivery systems maintain uniform drug levels, reduce dose, side effects, and increase the safety margin **(**Roy H. *et al*., 2013). Matrix controlled release tablet formulations are the most fashionable and straight forward to formulate on a commercial scale. A wide variety of polymer matrix systems have been used in oral controlled drug delivery to obtain a desirable drug release profile, cost effectiveness, and broad regulatory acceptance.

Matrix refers to a system where a drug is incorporated into a polymer(s) structure by either particle or molecular dispersion, where the former is a suspension of drug particles homogenously distributed in the polymer(s) structure and the latter drug molecules are dissolved in the polymer, where in the drug release occurs by diffusion through and/or erosion of the polymer structure (Görner T. *et al*., 1999). Granules are preparations consisting of solid, dry aggregates of powder particles sufficiently resistant to withstand handling. They are intended for oral administration. Some are swallowed as such; some are chewed and some are dissolved or dispersed in water or another suitable liquid before being administered. Granules contain one or more active substances with or without excipients and, if necessary, colouring matter authorised by the competent authority and flavouring substances. They are presented as single-dose or multidose preparations. Each dose of a multidose preparation is administered by means of a device suitable for measuring the quantity prescribed. For single-dose granules, each dose is enclosed in an individual container, for example a sachet or a vial. In other cases, thegranules are compressed to get the tablets. For the matrix type tablet dosage form, the matrix granules are prepared first. Suitable polymers, natural or synthetic can be employed for this purpose.

The natural polymers do hold advantages over the synthetic polymers, generally because they are nontoxic, less expensive, and freely available. Natural gums can also be modified to have tailor-made materials for drug delivery systems and thus can compete with the synthetic biodegradable excipients (Bhardwaj TR *et al*, 2000). Natural gums are natural polymers, which mainly consists of carbohydrates, small amounts of proteins and minerals. They are made from different parts of plants. They provide many applications in the formulation development of a new controlled release dosage

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form, such as binder, disintegrator, diluents and release modifier. Therefore, they need a novel approach to enhance the use of natural polysaccharides in the formulation development of controlled released dosage form, because of the ease availability at an affordable price, high safety margin and higher productivity (Sumathi S. et al., 2002). The gums are used very much in the food industry as thickeners and they are changing the viscosity significantly in low concentration.

Gum Karaya is a dried gummy exudate obtained from the tree *Sterculia urens*, belonging to the family Sterculiaceae. The swelling behavior of karaya gum is dependent upon the presence of acetyl groups in its structure. Deacetylation through alkali treatment results in a water soluble gum. When used in higher concentrations in water (up to 4%), karaya forms gels or pastes. Unlike other gums, karaya swells in 60% alcohol, but remains insoluble in other organic solvents. Karaya may absorb up to 100 times its weight in water (Vinod VTP. *et al.*, 2010). The major use of Gum Karaya is as a bulk laxative in view of its ability to form a mucilaginous gel on contact with water. For their use, the Gum is ground to a granule size of 8-30 mesh. These granules have a capacity to absorb and after and swell to 70-100% times their original value. The Gum is neither digested nor absorbed by the body. The Gum has also been used in a limited way as a wet end additive in paper manufacture in conjunction with starches. Gum Karaya is used extensively in various totally unrelated industries because of the properties such as water absorbing / moisture absorbing, gel and film forming, adhesiveness abilities. It is highly resistance to hydrolysis by mild acids and degradation by most of the microorganisms.

Amoxicillin (α-amino hydroxyl benzyl penicillin) is a semi synthetic antibiotic, belonging to the βLactam family, which is effective for bacterial infection treatment, especially for *Helicobacter pylori* infection. Helicobacter pylori is a major causative agent of diseases such as Tonsillitis, Pneumonia, Bronchitis, Gonorrhoea, ear infections, urinary tract infection and skin infection. It is a β-lactam antibiotic agent which is chemically 7-[2-amino-2-(4-hydroxyphenyl) - acetyl] amino-3, 3-dimethyl-6-oxo -2-thia-5-azabicyclo [3.2.0] heptane -4-carboxylic acid. Amoxicillin trihydrate acts by inhibiting the cross-linkage between the linear peptidoglycan polymer chains of the cell wall of grampositive bacteria such as *Streptococcus spp*., *Staphylococcus. spp.* and *Enterococcus spp.* and gram-negative organisms such as Haemophilus, Neisseria, Escherichia, Proteus and *Salmonella* spp (Verbeken D. *et al*., 2003) Amoxicillin in trihydrated form is available in capsules, chewable and dispersable tablets, and syrup and paediatric suspension, for oral use and as sodium salt for intravenous administration (Murali Mohan Babu G V. *et al.*, 2001).

MATERIALS and METHODS

Amoxicillin trihydrate (Unimerk Remedies, Birganj, Nepal) Gum karaya Powder # 150 (Nutriroma, Hyderabad, India) were gift sample. Lactose I.P. obtained commercially procured by the institution laboratories.

Drug-Excipient Interaction Study Using

FTIR Spectroscopy

Drug-excipient interaction, one of the most essential parameters, is studied before development of the formulations. Amoxicillin trihydrate, Gum karaya and its mixture with drug were mixed with IR grade KBr in the ratio 1: 100.Corresponding pellets were prepared by applying 5.5 metric ton of pressure in a hydraulic press. The pellets were scanned over a wave number range of 4000 to 400 cm^{-1} in FTIR spectroscope (ALPHA T, Bruker, USA).

Differential Scanning Calorimetry (DSC)

The DSC analysis of pure drug, Gum karaya, and physical mixture of the Gum karaya with the drug was carried out separately using Pyris Diamond TG/DTA Thermo gravimetric /Differential Thermal Analyzer (Perkin Elmer Inc, PerkinElmer SINGAPORE) to study any possible drug-polymer interaction at the molecular level. The ratio of drug to polymer chosen was same as that in the final formulation. Platinum crucible was used with alpha alumina powder as reference.

About 6 to 10mg sample were kept in platinum pans at a rate of 12°C/min from 10°C to 300°C temperature range under a nitrogen flow of 150 ml/min. The changes in the DSC curves were evaluated both with the positions of peak maxima and minima. The peak areas represent the phase-transition enthalpies **(**Mukherjee B. *et al*., 2009).

Preparation of the matrix granules

The matrix granules were prepared by wet gum method with different concentration of Gum karaya in water. Lactose was used as diluents. No other varying parameters were involved to prepare the granules.

Micromeritics Evaluation of granules

Micromeritics property of the granules like bulk density, tapped density, angle of repose, Carr's index, Hausner's ratio were measured and compared with the micromeritics property of API.

Swelling Index

The extent of swelling was measured in terms of % weight gain by the granules. The swelling behaviour of all formulation was studied. 2 gm from each formulation was kept in a petridish containing pH 6.8 phosphate buffers. At the end of 1 hour, the petridish along with the granules were weighed. Then weights of the granules, were noted, and the process was continued till the end of 24 hours (Vishnu MP. *et al*., 2007)

The swollen granules were weighed (W2) and the percentage of swelling was calculated by the following formula. Swelling index = (W2 - W1)/W1*100

Moisture content capacity

To determine the moisture content capacity of the granules they were kept in desiccators for 24 hours with Silica beads. The percentage moisture content was calculated from the weight differences relative to the final weight after exposing prepared matrix granules to activated silica in vacuum desiccators.

Drug Content Analysis

Accurately weighed 30mg of granules were crushed into fine powder. The powder was mixed with 100 mL phosphate buffer pH 6.8 in a volumetric flask, and the mixture was stirred for 48 h at room temperature using a magnetic stirrer (Remi Equipments, Mumbai, India). The drug content analysis for Amoxicillin trihydrate was done by UV method. Initially, the time of analysis of the method was standardized by taking formulation with measured amount of drug in phosphate bufferpH-6.8 and determination of amount of drug released with the duration. The absorbance was measured spectrophotometrically at λ_{max} 272 nm. It was found that 100% release of the drug was found by 24 h. Therefore, the time of drug content analysis was chosen up to 24 h (Ghosh S. et al., 2009).

The granules were taken in 100 mL phosphate buffer pH 6.8 in a volumetric flask, and the mixture was stirred for 48 h at room temperature using a magnetic stirrer (Remi Equipments, Mumbai, India). The drug content analysis for Amoxicillin trihydrate was done by UV method. Initially, the time of analysis of the method was standardized by taking formulation with measured amount of drug in phosphate buffer pH-6.8 and determination of amount of drug released with the duration. It was found that 100% release of the drug was found by 24 h. Therefore, the time of drug content analysis was chosen up to 24 h (Ghosh S. *et al*., 2009).

In vitro drug release (Dissolution Study)

The United States Pharmacopeia (USP) XXIII rotating paddle method used to study the drug release from the granules. The dissolution medium consisted of 900 ml of phosphate buffer pH 6.8. Accurately weighed 30mg of granules were considered for drug release study. The experiment was performed at 37°C ± 0.5°C, with a ro- tation speed of 50 rpm. Samples (5 mL) were withdrawn at predetermined time intervals and replaced with fresh medium. The samples filtered through Whatman filter paper and analyzed after appropriate dilution (1ml of Sample in 10 ml) by UV spectrophotometer (UV – 1800 Shimadzu) at 272 nm (pH- 6.8) **(**Mukherjee B *et al*., 2005)

Kinetics of Drug Release

To investigate the drug release kinetics from granules of Amoxicillin trihydrate the release rate obtained from dissolution studies were fitted to various kinetic equations. The kinetics models used were, zero order equation ($Qt = Q_0 – K_0t$), First order equation ($Q_t = lnQ_0 - K_0t$) and Higuchi's equation ($Q_t = Kht_{1/2}$).

Statistics

Data were assessed by one-way ANOVA followed by

Table 1: Composition, Drug content and Moisture content of the matrix granules

Batch No	Gum karaya (Concentration %)	Drug content	Moisture content
F1	2.5	99.11 ± 0.6 %	7.17%
F2	5	98.09 ± 0.6 %	10.06%
F3	7.5	98.17 ± 0.6 %	11.79%
F4	10	98.18 ± 0.6 %	13.77%
F5	12.5	98.19 ± 0.6 %	14.13%
F6	15	98.16 ± 0.4 %	15.61%
F7	17.5	98.17 ± 0.6 %	15.88%
F8	20	98.23 ± 0.4 %	17.40%

Data show mean (n=6) ± SD

Table 2: Release rate constants for the drug Amoxicillin trihydrate from the matrix granules obtained from different kinetic models

Batch	Zero Order		First order		Higuchi	
	R^2	K_1	R^2	K_2	R^2	K_3
F1	0.9771	0.0872	0.943	1.629	0.990	2.721
F2	0.9733	0.0882	0.949	1.231	0.975	2.718
F3	0.9721	0.0871	0.946	1.611	0.976	2.703
F4	0.9743	0.0952	0.9903	1.001	0.9443	2.977
F5	0.993	0.0851	0.960	1.514	0.981	2.61
F6	0.9916	0.0587	0.9798	1.001	0.9744	1.727
F7	0.980	0.0582	0.925	1.303	0.986	1.726
F8	0.9759	0.06	0.9175	1.14	0.9987	1.824

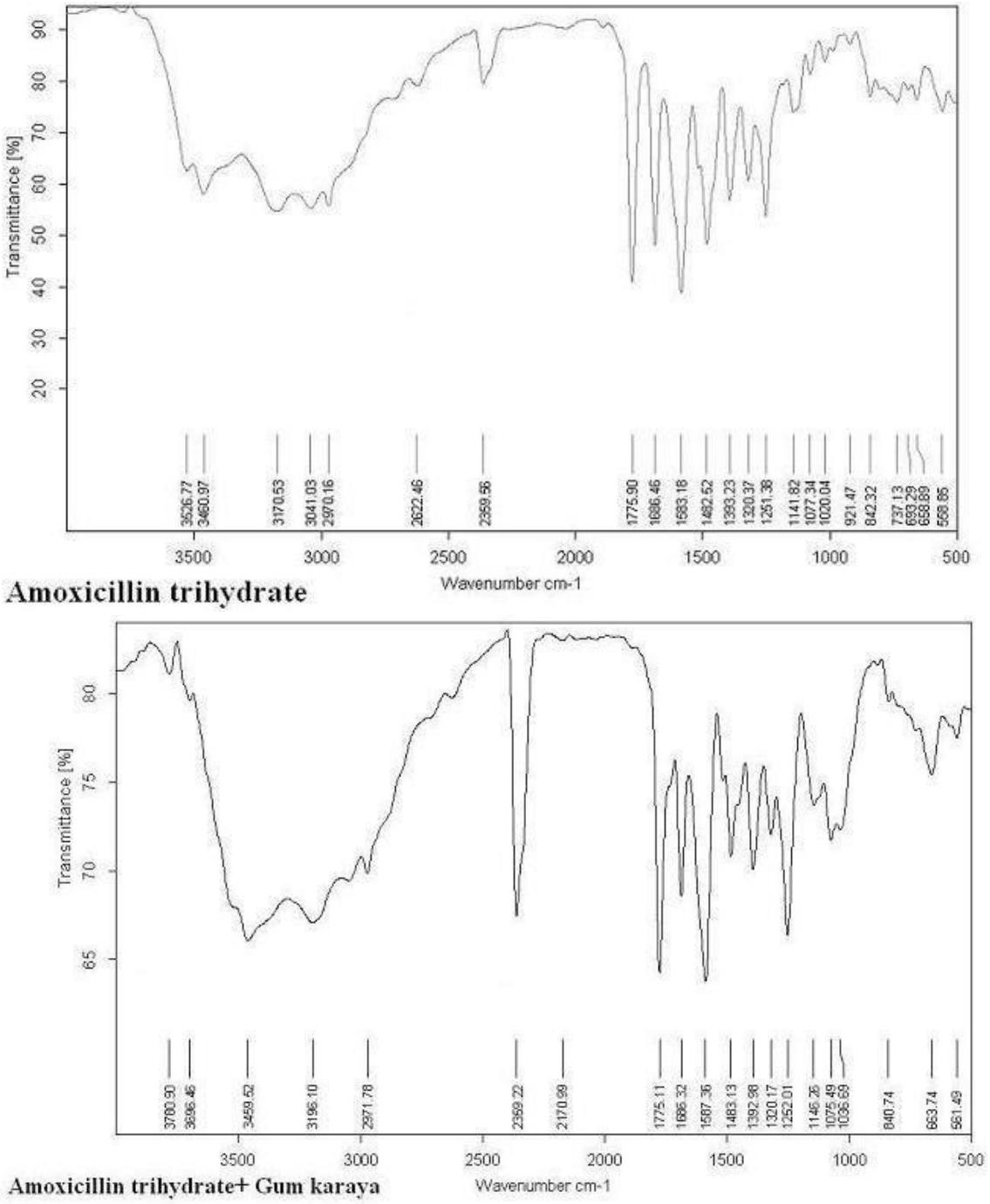

Figure 1: FTIR spectra of a. Amoxicillin trihydrate b. mixture of Amoxicillin trihydrate and Gum karaya

Tukey HSD Test using Vassar Stats software (USA). P<0.01 has been considered as statistical significance.

RESULTS AND DISCUSSION

The present study was intended to develop controlled release granules containing the drug-polymer ratio by weight was taken 1:10 for each of the formulations. Drug-excipient interaction is a very important pre-formulation study to develop a new formulation (Bruni G. *et al*., 2002). Among the various methodologies available to understand the drug excipient interaction, common approaches are FTIR spectroscopy, DSC, IR-spectra etc. FTIR-spectroscopy shows the interaction between the molecules at the level of functional groups. Here drug-excipient interaction was studied using FTIR-spectroscopy and DSC. An FTIR spectrum of pure Amoxicillin trihydrate shows that all the characteristic peaks of Amoxicillin trihydrate are present. Figures (1A, 1B) show the IR spectra of drug and mixture of drug and polymer respectively. Between 3200 cm^{-1} and 2800 cm^{-1} and between 1800 cm^{-1} and 1000 cm^{-1} wave numbers, variations at transmission spectroscopy data were noted. Alkenyl (-C=C-) (3020 cm^{-1}-3100 cm^{-1}), amide (-NH) (1000 cm^{-1} - 1250 cm^{-1}) ketonyl (-C=O) (1710 cm^{-1} -1720 cm^{-1}), phenolic (-OH) (970 cm^{-1} -1250 cm^{-1}) stretches are mainly responsible for those regions. This suggests that there may be physical interactions related to the formation of weak

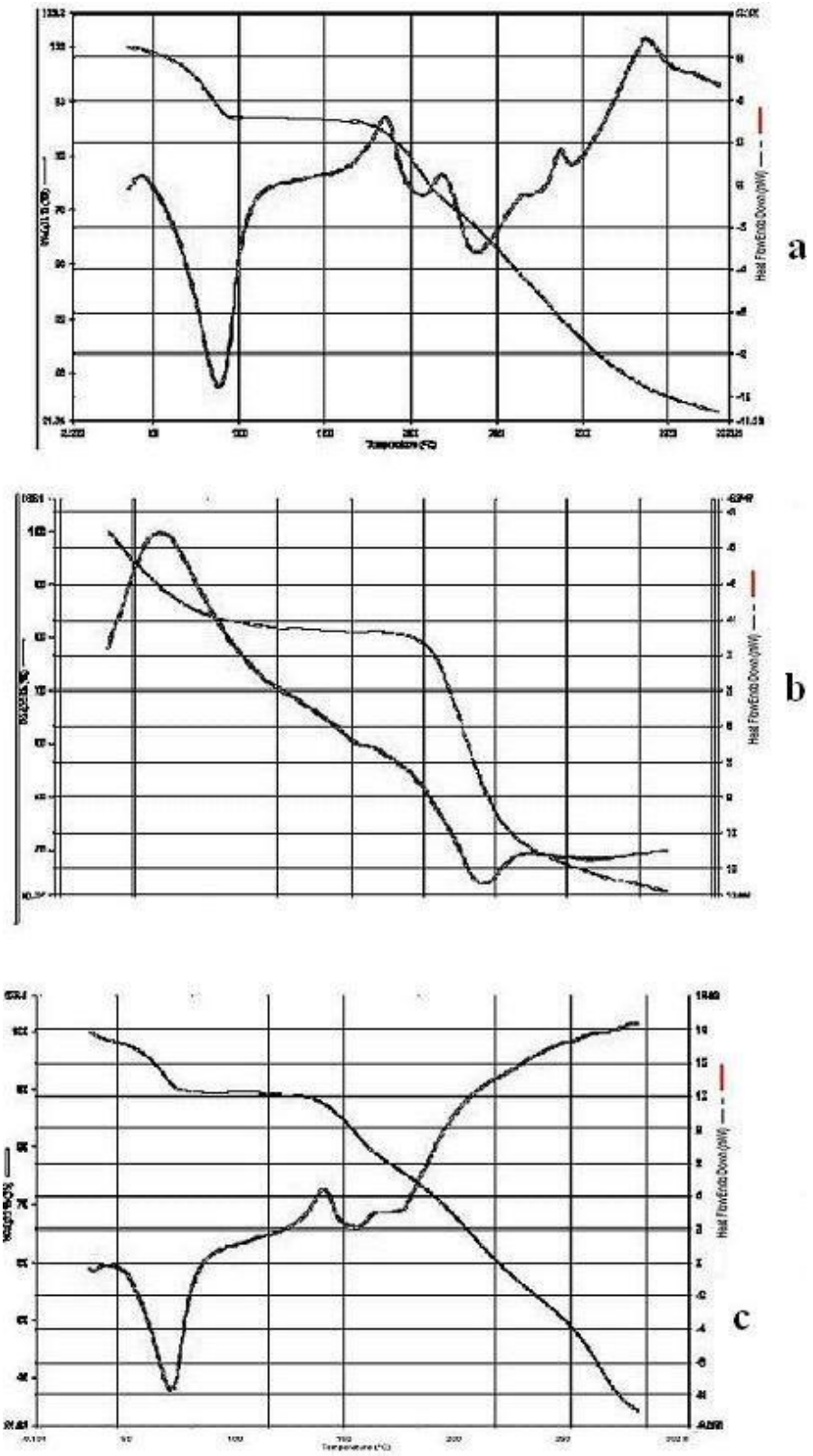

Figure 2: DSC and thermograms of a. Amoxicillin trihydrate b. Gum karaya c. mixture of Amoxicillin trihydrate and Gum karaya

to medium intensity bonding since no major shifting of peaks was noted. Polymers may change the rate and pathway of diffusion of drug molecules by varying entanglement in polymeric network. Thus the physical interactions might be helpful in sustaining the release of drug molecules from the experimental formulations.

DSC measurement was carried out to provide better evidences whether predicted physical interaction would lead to drug amorphous formation in the formulations. Figure 2A shows the DSC and TGA of Amoxicillin trihydrate. Figure 2B and 2C Show the DSC and TGA

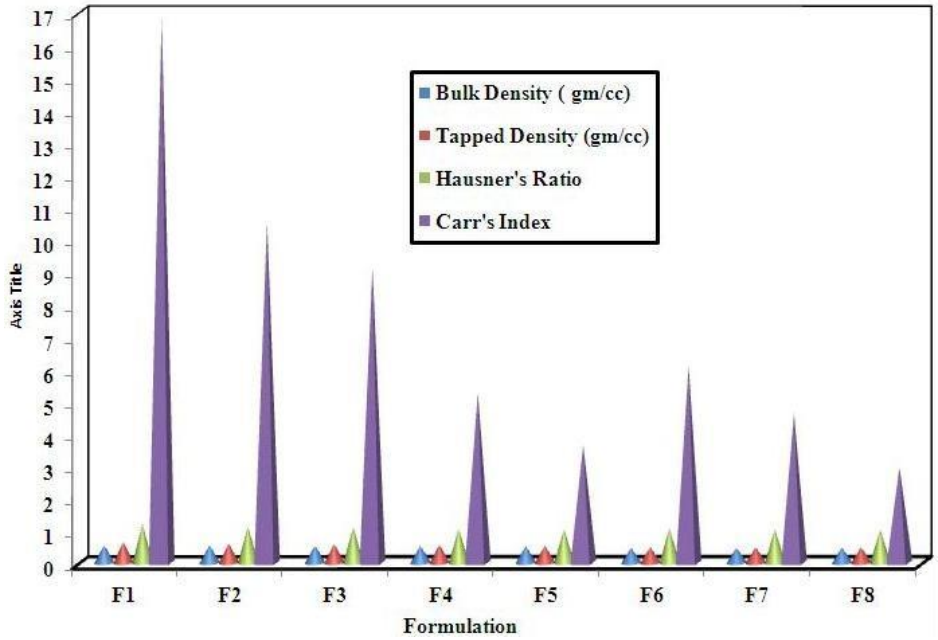

Figure 3: Micromeritics properties of the matrix granules

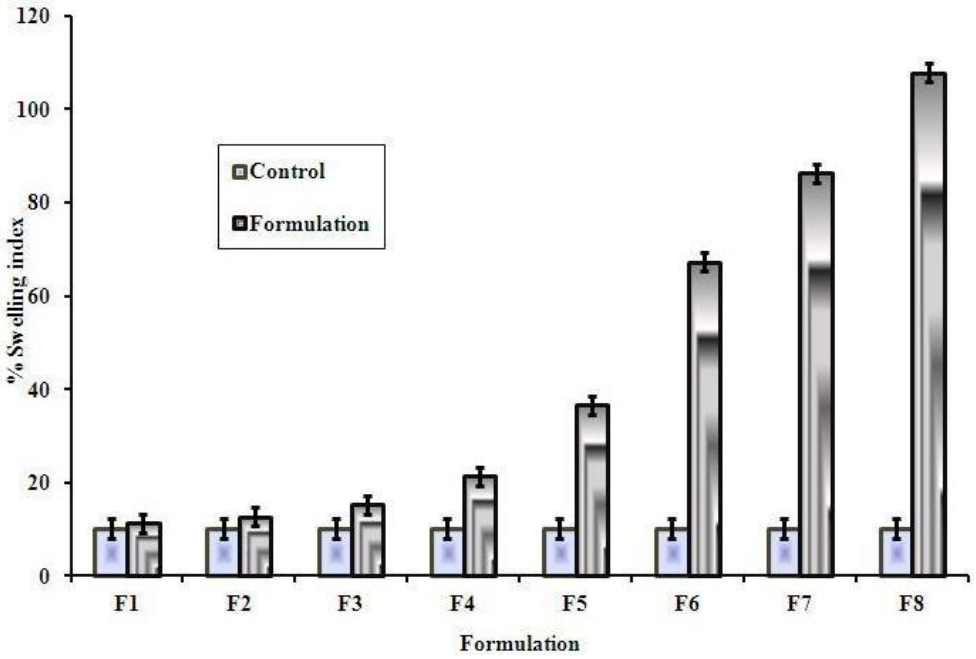

Figure 4: Swelling index in terms of water absorption capacity of matrix granules at phosphate buffer pH-6.8 for 4 h. Data show mean (n=6) ± SD

of Gum karaya and Drug-Gum karaya mixture respectively.

Figure 2C shows dipping of curve at 84.27°C claiming the loss of water molecule from Amoxicillin trihydrate. This was followed by the crystallization of Amoxicillin trihydrate molecules at 182°C and then immediately it was followed by the melting of the drug molecules at 194°C. When the drug molecules reached at 182°C they gained enough energy to move into very ordered arrangement for crystallization. Thus 182°C temperature gave the crystallization temperature of Amoxicillin trihydrate. This was followed by endothermic transition of melting phenomenon started at 194°C and this was followed by degradation of the molecules. The data are further supported by TGA curve of the drug in the same Figure. The changes in all the DSC thermograms correspond to the changes at the respective TGA shown in the Figure 2.

The granules show satisfactory physical-mechanical properties (Table 1). In the entire eight formulations drug content is above 98% and the low values of standard deviation and coefficient of variation (<1) indicate uniform distribution of the drug within the granules. The result of moisture content was 7.17% to 17.40%.

Micromeritics properties involve the study of small particles and of the order of a few microns size. This study involves the characterisation of individual parti-

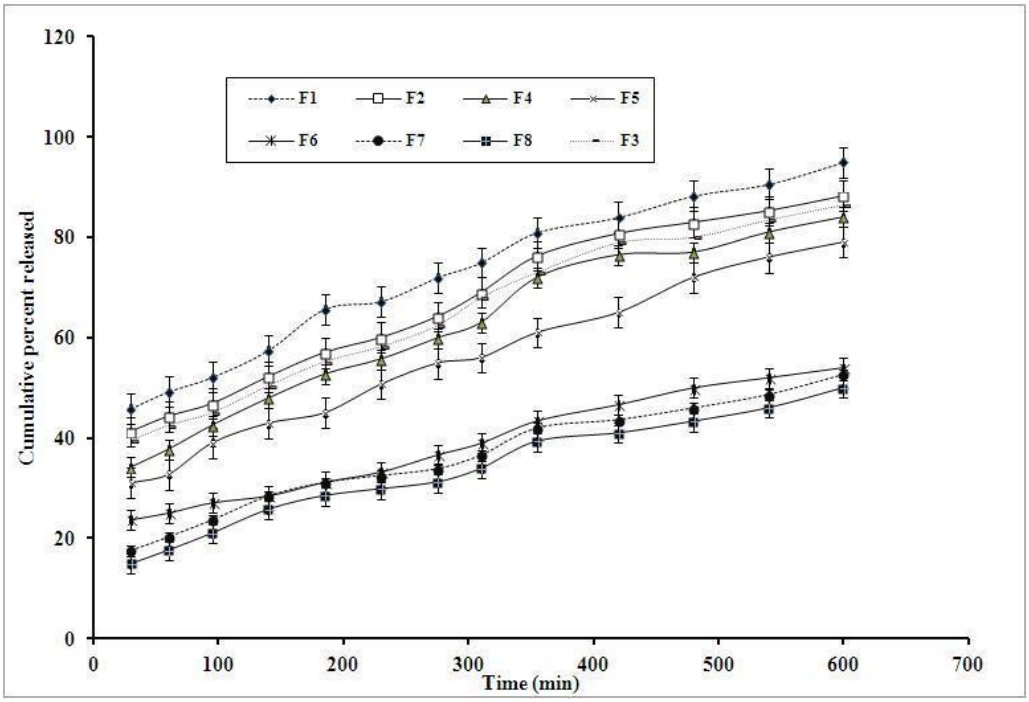

Figure 5: In vitro release of Amoxicillin trihydrate from matrix granules containing Amoxicillin trihydrate in phosphate buffer (pH-6.8)

Data show mean (n=6) ± SD, Values were significantly different as accessed by one-way ANOVA followed by Tukey HSD test ($p<0.01$)

cles, particle size distribution and powders. The size, and hence the surface area of a particle, can be related to the physical, chemical and pharmacologic properties of drugs. Clinically, the particle size of a drug can affect its release from dosage forms. Here all the micromeritics properties like Bulk density, Tapped density, compressibility or Carr's index, Hausner's ratio were within the acceptable limits. The values (Figure 3) indicate that the granules of all the formulations except F1 and F2 possess excellent flow properties.

Swelling depends on the polymer concentration and the moisture absorption capacity of the polymers (Moustafine RI. *et al*., 2008). The swelling results (Figure 4) were expressed in terms of percentage water uptake at 37°C. For F6 the swelling was 51.43 % and for F1 and F8 they were 10.35 % and 107.85 % respectively. The swelling ability increases with increase in percentage of Gum karaya. The highest hydration (swelling) was observed with the formulation F8. Flexibility of polymer chain from individual polymer is important for interpenetration and entanglement. In presence of water molecules, polymers become crosslinked and the mobility of individual polymer chain decreases thus swelling occurs with the time.

Figure 5 represents the graph consisting of cumulative percentage of drug release vs time. Drug release is the slowest one in F8. In formulation F4, $t_{50\%}$ value is 2 hr 35 minutes whereas in F6 and F8 they are 8 hr and 10 hr 5 minutes respectively.

The release profile and kinetics of drug release are important because they correlate the in vitro and in vivo drug responses by comparing results of pharmacokinetics and dissolution profile patterns. Hence, the cumulative drug release results of the formulations were fixed into various mathematical models.

The drug release pattern of formulation F4, F5and F6 was found to be highly linear, and close to infinity as indicated by their high regression value (r^2) as 0.9843, 0.9930 and 0.9916 respectively. Therefore it was ascertained that the drug release from these formulations could follow either zero or near zero order kinetics. These forms released the same amount of drug by unit of time irrespective of the drug concentration. F1, F2 and F3 drug release followed mixed kinetics. The results are presented in Table 2. It was noted that drug release gradually changed from concentration independent "zero-order" release kinetics to concentration dependent "first-order" kinetic pattern. At the beginning, because of the matrix structure drugs is released by zero-order kinetic pattern later due to erosion of the structure drug released via first order kinetics where as F7 and F8 followed Higuchi kinetics throughout the study (r^2=0.9860 and 0.9987 respectively). Here more amount of Gum karaya is responsible for maximum swelling of the matrix. That swollen layer behaves like a complete matrix structure and controlled the drug release showing Higuchi kinetics of drug release as with the time, the swelling of the polymers varied the entanglement of polymeric pathways to control the diffusion of the drugs from the formulations (Aalaie J. *et al*., 2009). In F4, F5and F6 drug release is concentration independent -zero order. Here concentration of Gum karaya was such that it showed

promising drug release pattern. That was optimum enough to hold the matrix structure till the experimental work to release the drug in zero order fashion.

CONCLUSION

The granules with 10, 12.5 and 15 % concentration of Gum karaya showed zero order kinetics of drug release when subjected to dissolution study in phosphate buffer pH-6.8. It leads to the conclusion that the matrix granules can be compressed to tablet to get a successful oral controlled release formulation.

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