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Effect of Submicron-Acacia Gum on Carbamazepine Release vs. Marketed Formulations

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Abstract: The pharmaceutical industry is always searching for new solutions to increase solubility and, consequently, the release and pharmacological activity of gentle biopharmaceutical classification system (BCS) class II compounds. Carbamazepine (CBZ) is used as an anticonvulsant and to treat mood disturbances; however, its low water solubility results in low bioavailability and fluctuating plasma concentrations. To overcome these challenges, new formulations leveraging nanotechnology have shown promise. This study aimed to investigate the effect of acacia gum on the solubility of carbamazepine, as a model drug. Carbamazepine nanoparticles were formulated using two viscosity grades of guar gum, acacia gum, and polyvinylpyrrolidone through the emulsification/solvent evaporation method. We compared the prepared tablet with the commercial formulation using characterisation tests, including hardness, friability, assay, and drug release. The drug release profile of the developed tablet (40% drug release) differed significantly from that of the commercial tablet (100% drug release). Acacia gum exerted substantial control over drug particles, and the gum's crosslinking effect appeared more efficient, leading to decreased drug solubility and dissolution. The data illustrated in this research prove the specificity of acacia gum in controlling the extent of carbamazepine dissolution and release. Also, the lower dissolution rate of the developed tablet compared to the marketed tablet suggests that acacia gum's crosslinking behaviour may contribute to a controlled-release mechanism, slowing the drug's dissolution.

Keywords: polymers, nanoparticles, acacia gum, carbamazepine, drug release

INTRODUCTION

Nanotechnology employs curative agents at the nanoscale level to develop nanomedicines. As a technique, nanotechnology has enabled the enhancement of solubility, dissolution rate, and, consequently, the bioavailability of poorly aqueous-soluble drugs. Hence, they can move more freely within the human body than microscale-sized molecules. Nanoscale-sized particles exhibit unique structural, chemical, mechanical, magnetic, electrical, and biological properties [1, 2]. Polymer-based hydrogels are soft materials composed of three-dimensional polymer networks that can absorb and retain large amounts of water or biological fluids while maintaining structural integrity [3].

This work builds upon previously published research [4], in which carbamazepine submicron particles were produced using two viscosity grades of polymers (guar gum, acacia gum, and polyvinyl pyrrolidine) via an emulsification/solvent evaporation technique. The resulting particles from the first portion of all 24 runs were qualified for particle diameter, polydispersity index (PDI%), zeta potential, entrapment efficiency (EE%), drug loading, and

drug release investigations [4-6]. It was concluded that Run8, which contains submicron particles of higher-viscosity acacia and 1% carbamazepine, has the best ranking properties. The study was then extended to investigate these particles further. The particles were compressed into tablets to evaluate the impact of formulation factors on their properties and to compare their performance with that of marketed tablets.

Acacia Gum is the dried exudate of the acacia tree (*Acacia senegal* or related species of Acacia Fam. Leguminosae). It's a complex mixture of Ca, Mg, and K salts of Arabic acid (a complex, highly branched polysaccharide colloid) that contains galactose, rhamnose, glucuronic acid, 4-O-methyl glucuronic acid, and arabinose residues. It has a broad molecular weight distribution.

The Use of acacia gum as a biodegradable nanocarrier has been extensively investigated for drug delivery applications due to its biocompatibility, biodegradability, and emulsification capacity [7]. Acacia gum is known for forming stable colloidal dispersions, making it a promising candidate for the encapsulation of poorly soluble drugs. Moreover, its mucoadhesive properties enable sustained drug delivery in the gastrointestinal tract and improve its bioavailability. Acacia gum has been used in various nanoparticulate drug delivery systems and has shown some effectiveness in improving the solubility and bioavailability of drugs such as carbamazepine (CBZ). Patil *et al*. [8] conducted a study comparing the efficiency of acacia gum in dispersing CBZ to produce strong solid dispersions. The findings showed that the dissolution rate of CBZ was enhanced by various physical techniques that increased wettability, and that a larger drug surface area was responsible for the enhancements. Thus, Sharma *et al*. [7] found that the dissolution rates of CBZ nanoparticles with gum Acacia as a stabilizer are higher than the regular forms of CBZ. Nano-sizing and achieving submicron particle size improved the drug's release profile, enhancing its bioavailability and therapeutic efficacy [9].

Carbamazepine is a dibenzoazepine derivative with antiepileptic and psychotropic properties. A white or almost white crystalline powder. It exhibits polymorphisms that are very slightly soluble in water, sparingly soluble in alcohol and in acetone, and freely soluble in dichloromethane.

Although carbamazepine has a high intestinal permeability, its bioavailability is limited by its low water solubility (0.11mg/mL) [10]. It is extensively metabolized in the liver, notably by the cytochrome P450 isoenzymes CYP3A4 and CYP2C8. One of its primary metabolites, carbamazepine-10, 11-epoxide, is also active. Carbamazepine is excreted in the urine almost entirely in the form of its metabolites; some are also excreted in feces. Elimination of carbamazepine is reported to be more rapid in children, and accumulation of the active metabolite may often be higher than in adults [9]. Carbamazepine is widely distributed throughout the body and is about 70-80% bound to plasma proteins. It induces its own metabolism, so that the plasma half-life may be considerably reduced after repeated dosing. The mean plasma half-life of carbamazepine on repeated dosage is about 12 to 24 hours; it appears to be significantly shorter in children than in adults.

MATERIALS AND METHODS

Materials

Table 1 shows the description of the materials used in this research as received.

Table 1: Materials.

Material	Manufacturer and Source
Carbamazepine	Bajaj Health Care Ltd, Aljazeera Pharm Co. (KSA)
Acacia gum (128cps)	Panreac (Germany), Aljazeera Pharm. Co. (KSA)
Avicel	Foremost (USA), Aljazeera Pharm. Co. (KSA)
Aerosill	Evonik Industries (Germany), Aljazeera Pharm. Co. (KSA)
Carbamazepine 200 mg conventional tablets	purchased from the local market

Methods

Tablet Formulation

Based on previous findings [4], the composite index identified run 8 (the developed formula) as the optimal formulation, containing 1% high-viscosity acacia with carbamazepine, which met all the required criteria for tablet preparation. In this instance, particles (2762.69 nm) composed of 1:1 carbamazepine and 1% w/w 128 cps viscosity grade acacia were thoroughly mixed with microcrystalline cellulose (Avicel) at a 1:1 ratio with the drug. Then colloidal silicon dioxide (Aerosil) was added through an 80-mesh sieve and blended. The formed blend was then processed into 12 mm diameter tablets using a direct compression technique, yielding tablets weighing an average of 400 mg and containing 200 mg of drug per unit dosage.

Tablet Characterization

The tablets produced across all batches were subjected to hardness, friability, drug content, and drug release specifications (time and concentration).

Hardness and Friability:

The diametrical crushing strength test was performed on 10 tablets from each formulation, where tablets were tested in a hardness tester (Caleva® THT, China) that measures the force required to break the tablet in kg/cm^2. Moreover, the sample of 10 tablets was tested for friability, in which the tablets were weighed and tested in a friability tester (ERWEKA® TA, Germany) rotating at 25 rpm for 4 min. After removing the dust, tablets were re-weighed, and friability percentage was calculated using the ratio (as a percentage) of the difference in the total tablets' weight before and after the test to the total weight of tablets before the test [11].

Assay of Tablet Formulation:

Twenty tablets were accurately weighed, the average weight was calculated, and the tablets were then crushed into fine powder. The powder equivalent to 50 mg CBZ was transferred into a 50 mL volumetric flask, sonicated to dissolve in 30 mL of methanol, and the volume was completed with methanol. The solution was filtered using Whatman® filter

paper, further diluted with distilled water to obtain a final concentration of 10 µg/ml, and then subjected to UV analysis at 287nm. This procedure was repeated in triplicate [12, 13].

Drug Release Profile:

The drug-release study was carried out using a USP basket apparatus at 37±0.5°C and 75 rpm, with 900 mL of 0.1N SLS (sodium lauryl sulphate) as the dissolution medium. For each batch (developed formula and marketed tablet), six tablets were tested, and a 5 mL sample solution was withdrawn at predetermined time intervals, filtered, and analyzed for CBZ spectrophotometrically (double-beam UV-1800, Shimadzu, Japan) at 287 nm. Jani fully described the methods [14]. The amount of drug released was calculated using a pre-calibrated calibration curve. Finally, A comparative study of drug release from developed submicron particle-based CBZ tablets and marketed conventional CBZ tablets, each containing 200 mg of loaded drug, was performed using the statistical dissimilarity factor (*f1*).

RESULTS AND DISCUSSION

Tablets Formulation and Characterization

Table 2 recapitulates different properties of the compressed mass of formulation R8

The As shown in Table 2 the formulated tablets pass the official test with moderately high crushing force strengths which can be attributed to the higher content of acacia which acts as a binder (tablets contain 200 mg particles and each particle contain 1:1 drug-polymer ratio so actually it contains 200 mg acacia plus microcrystalline cellulose(Avicel) and colloidal silicon dioxide (Aerosil)), as result of this the drug release has been effected as shown in figure 1. A slow drug release can be seen in the first hour, with less than 40% release in 60 minutes. This result is entirely different from the particle release rate of the developed formula as in the previous study [4], more than 50% of the drug was released in 60 minutes, which can be explained by the effect of compression force that was applied during tablet formulation and the increased hardness of the tablets, and accordingly retard drug release. The best-fit model for the release profile is the Korsmeyer-Peppas Equation with a Diffusion exponent (*n*) = 1.02 [15].

Table 2: Properties of compressed mass of formulation run 8.

Property	Values
Drug content per tablet	200 mg
Friability	0.03%
Hardness	7.24 kg/cm2
Drug release at 60 min (%Rel60min)	28%
Diffusion exponent (n)	1.02 (r2 =0.9968)

Determination of Drug Release Kinetics

The *in vitro* release data of loaded drugs from tablet formulations were analyzed using PCP Disso software to verify the release kinetics. Fitting data are summarized in Table 3

Table 3: Carbamazepine release and similarity attributes of marketed and R8 tablet forms.

Attribute	Marketed tablets	R8 tablets
Dissolution efficiency at 60 min (DE_{60min})	0.82	0.14
Time for 25% drug release ($T_{25\%}$)	4 min	55 min
dissimilarity factor (*f1*)	5.2	

Comparison of Drug-marketed Tablets with Developed Formula Tablets

Figure 1 shows carbamazepine release profiles from marketed and developed formula drug tablet formulations.

The drug-release profile of the new formula was compared with that of the marketed tablet. As shown in Figure 1, the new formula has a different release profile. The marketed tablet releases the drug completely (100%) within the first 60 minutes, while the new formula releases carbamazepine much more slowly.

The application of acacia gum has a significant influence, resulting in greatly restricted drug particle movement. Acacia gum reduces the dissolution rate of CBZ by forming crosslinked particles.

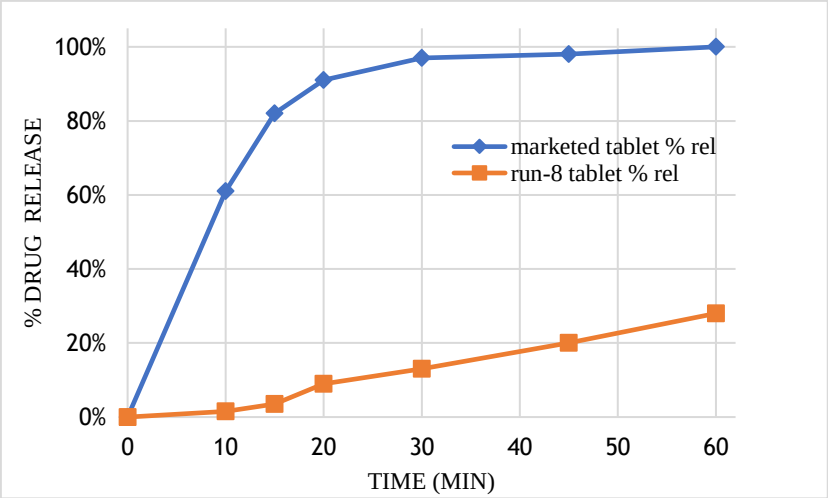

Fig. 1: Release profile of carbamazepine from marketed and R8 tablet formulations. Each data point is an average of 3 determinations.

Effect of Acacia Gum on Drug Release

The pharmaceutical industry uses acacia gum as an essential natural polysaccharide because it forms effective gels while stabilising colloids. Acacia gum significantly affects carbamazepine drug release in the developed formula, as its dissolution rate under these conditions is notably slower than that of the current commercial tablet. Polymer-based hydrogels can regulate the release of drugs by controlling their swelling behaviour, leading to sustained drug delivery for a long time [16]. When loaded with drugs, hydrogels can hold them within their porous structure, gradually releasing them in a controlled manner [17]. On the other hand, the crosslinking interactions between acacia gum create more rigid

structures that surround drug particles and reduce drug solubility and retard drug dissolution [8]. A recorded delay in CBZ release becomes possible because of this drug-polymer interaction. The developed formula demonstrates drug release controlled by its rigid structure, thereby extending the duration of drug release. Moreover, the slower release observed with the developed formula could indicate that the drug's release in the gastric media is controlled by a matrix-based system, suggesting that the drug provides extended therapeutic effects. This was achieved by comparing it with the commercial formulation. Acacia gum shows potential as a natural material for controlled drug delivery approaches compatible with current formulation systems. The commercial carbamazepine tablet, on the other hand, shows a consistent and fast drug dissolution percentage, and it reaches 100% within 60 min only. Traditional immediate-release dosage forms typically dissolve and release the active pharmaceutical ingredient rapidly in the gastrointestinal tract. Though, as discussed, the fast release in the commercial tablet might not be suitable for drugs that don't dissolve well, like carbamazepine. The drug might not dissolve in stomach fluids, resulting in suboptimal bioavailability and potentially different therapeutic effects [18].

Effects of Reduction in Drug Release Rate for Carbamazepine Preparations

The effect of acacia gum in the developed formula may increase the bioavailability and duration of action of carbamazepine, thereby improving patients' compliance [7, 19]. Still, the slower drug release rate observed in the developed formula suggests that other formulation factors, such as acacia gum concentration, need to be fine-tuned to achieve the desired release rate while ensuring proper drug dissolution. The main challenge lies in balancing the drug's solubility within the absorption sites (the small intestine and the gastrointestinal tract) while maintaining sustained release. Further experiments are needed to refine the formulation and achieve improved results.

CONCLUSION

Acacia gum specifically controls both dissolution and release kinetics of carbamazepine. The developed formula showed a slower drug dissolution rate than the marketed version, likely due to its crosslinking nature, which may act as a controlled-release mechanism. The controlled substance release proves beneficial for prolonged treatment, yet requires additional attention to achieve suitable drug absorption levels from the body. The development of optimized acacia gum-based products requires further investigation. Where acacia gum formulations achieve the desired release control, it will be vital to maintain sufficient solubility to enhance carbamazepine's bioavailability and therapeutic outcomes.

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Conflict of Interest

The authors declare no known financial or personal conflicts of interest that could have influenced the work reported in this paper.

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