

Solubility and Dissolution Rate Enhancement of Licofelone by Using Modified Guar Gum

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Abstract: Solubilization of poorly soluble drugs is a frequently encountered challenge in screening studies of new chemical entities as well as in formulation design and development. Many drugs have an aqueous solubility of less than 1 mg/l. These drug molecules are often lipophilic and hence dissolution may be rate limiting step in drug absorption from solid oral dosage forms. The increasing interest of the technology of dosage form with natural biopolymers has become the reason for undertaking present investigation on the possibility of guar gum application in the preparation of an oral solid dosage form of a poorly water soluble drug. Present study examines the effect of Guar gum (GG) and Modified guar gum (MGG) on the solubility of a poorly water-soluble class II drug licofelone. Modified guar gum (MGG) was prepared using heat treatment (125-130°C for 2 to 3 hours) method. It was characterized for viscosity, swelling index and water retention capacity. The physical and co-grinding mixtures of licofelone with GG and MGG were prepared in 1:6 drug to gum ratio. The physical and co-grinding mixtures were characterized by DSC and FT-IR study. The studies confirmed that there was no interaction between drug and carrier. Prepared mixtures were evaluated for solubility study and in vitro dissolution studies using USP XXIII Dissolution apparatus. The results of present investigation indicated that co-grinding mixture of licofelone with modified guar gum could be useful in developing an oral dosage form with increased solubility and hence improved dissolution and oral bioavailability of poorly water soluble drug.

Key words: Solubility enhancement, Dissolution rate, Guar gum, Modified guar gum.

Introduction

Product development scientists often encounter significant difficulties in solving the problem of poor water solubility of drug candidates in the development of pharmaceutical dosage forms. As a matter of fact, more than one-third of the drugs listed in the U.S. Pharmacopoeia fall into the poorly water soluble or water-insoluble categories. More than 41% of the failures in new drug development have been attributed to poor biopharmaceutical properties, including water insolubility.¹

It is commonly recognized in the pharmaceutical industry that on average more than 40% of newly

discovered drug candidates are poorly water soluble. Poor "drug like" properties of lead compounds led to ineffective absorption at the site of administration, which has been designated as an important part of the high clinical failure due to poor pharmacokinetics.

In the past two decades, with the applications of genomics, high-throughput screening, robotics, combinatorial chemistry, informatics and miniaturization to the drug discovery area, far more drug candidates than ever have been generated for development. Water insolubility can postpone or completely halt new drug development, and can

prevent the much needed reformulation of currently marketed products.²

Interpretation of the term “water-insoluble drug” can vary, depending on an individual’s definition. According to USP30/NF25, “slightly soluble” is defined as “one part of solute can be solubilized by 100 to 1000 parts of solvent.” If water is the solvent, then the water solubility of a “slightly soluble” drug can range from 10mg/ml down to 1mg/ml. If the same assumption is applied, “very slightly soluble” and “practically insoluble” can be translated to 1 mg/ml down to 100µg/ml, and equal to or less than 100µg/ml, respectively. Therefore, in the broader definition, the term “water-insoluble drug” in this book is defined as the aqueous solubility of a drug that falls into the range of “slightly soluble and below (i.e. <10mg/mL). In the narrower definitions, the term “water insoluble drug” indicates that the aqueous solubility of a drug belongs to the category of “practically insoluble or insoluble” (i.e. <100g/mL).

The solubility issues complicating the delivery of these new drugs also affect the delivery of many existing drugs. The main possibilities for improving dissolution according to Noyes-Whitney equation are to increase the surface area available for dissolution by decreasing the particle size of the solid compound and/or by optimizing the wetting characteristics of the compound surface, to decrease the boundary layer thickness, to ensure sink conditions for dissolution and, last but definitely not least, to improve the apparent solubility of the drug under physiologically relevant conditions.³ Traditional approaches to drug solubilization include either chemical or mechanical modification of the drug molecule, or physically altering the macromolecular characteristics of aggregated drug particles.⁴

Licofelone is a dual cox/lox inhibitor, belonging to the category of analgesic and anti-inflammatory. Inhibition of 5-lox may reduce the gastrointestinal toxicity associated with other nonsteroidal anti-inflammatory drugs which only inhibits cox (cyclooxygenase). Licofelone is the first drug to inhibit both. But licofelone is crystalline in nature and have very slightly solubility in water which limits its dissolution rates. This properties of licofelone makes it an interesting candidate for solubility enhancement studies.

The usage of natural polymers as drug carriers is on increasing side because of their low cost, biocompatibility and biodegradability. Guar Gum is a natural gum ground endosperm of the seeds from *Cyamopsis tetragonolobus* (L.) Taub. Belonging to family ‘Leguminosae’, mainly consisting of high molecular weight (50,000-8,000,000) polysaccharides composed of galactomannans; mannose: galactose ratio is about 2:1.⁶ The wider application of Guar gum

is due to its unique features such as high swelling and water retention capacity, high viscosity properties and abundant availability. Guar gum is used in solid-dosage forms as a binder and disintegrant. However, it is reported that the swelling ability of the carrier profound influence on the improvement of dissolution rate of poorly water-soluble drugs.⁷

Materials and Methods

Materials

Licofelone was obtained as gift sample from Macleods Pharmaceuticals Ltd, sarigam, valsad Gujarat, Guar gum (GG) was obtained from sigma Aldrich, and other ingredients were used for study were of commercial grade, purchased from SD. Fine chemicals, Bombay.

Methods

Preparation of Modified Guar Gum

Preparation of MGG was done by heating method. Briefly, powdered gum was taken in a porcelain bowl and subjected to heating using sand bath for different time periods at different temperatures. The results of swelling capacity and viscosity studies revealed that the modified forms possessed swelling property similar to GG, but viscosity was decreased as a function of temperature and time period of heating. However, it was observed that GG samples were charred, when heated at and above 150 °C. In the preparation of modified form of GG, no further change in viscosity of GG was observed by heating it at 125 °C for more than 2 h. Hence, the conditions of heating at 125 °C for 2 h were selected to prepare modified form of GG. The prepared modified form of GG was finally re-sieved (100 mesh) and stored in airtight container at 25 °C.⁸

Characterization OF GG AND MGG

Swelling and Water Retention Capacity

The swelling and water retention capacity of the GG and MGG were estimated by a slightly modified method.^{9, 10} About 1.0 g of GG powder was accurately weighed and transferred to a 100 ml stoppered measuring cylinder. The initial volume of the powder in the measuring 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 GG/MGG was expressed in terms of swelling index as follows. Swelling index (SI) was expressed as a percentage and calculated according to the following equation:

$$SI = \left(\frac{X_t - X_0}{X_0} \right) \times 100$$

Where, X_0 is the initial height of the powder in graduated cylinder and X_t denotes the height occupied by swollen gum after 24 h. 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 polysaccharide.

Viscosity Measurement

The viscosity of 1% (w/v) GG/MGG solution was measured according to the USP XXX, NF XXIV, at 37 °C using a Brookfield, DV-II Pro Viscometer and Spindle 62 (LV2).¹¹

Preparation of Co-Grinding Mixtures

Co-grinding mixtures (CM) of licofelone and GG or MGG were obtained by grinding a physical mixture of LICOFEONE and GG or MGG in a 1:6 weight ratio for 20 minutes in a ceramic mortar and sieved through 100 mesh. "CM-GG" represents the co-grinding mixture of licofelone and GG, and "CM-MGG" represents the co-grinding mixture of licofelone and MGG. To ascertain the effect of method, carrier, or both on the dissolution rate of licofelone, licofelone alone was ground for 20 minutes and the resultant product represented as licofelone 1. All the samples were stored in a desiccator at room temperature.¹²

Preparation of Physical Mixtures

The physical mixtures of licofelone and GG or MGG were obtained by blending the licofelone and GG or MGG in a 1:6 w/w ratio (drug: polymer) in an pilot scale double cone blender. PM-GG and PM-MGG represents the physical mixtures respectively.

Compatibility Study of Co-Grinding and Physical Mixtures

Differential Scanning Calorimetry

Differential scanning calorimetry (DSC) curves were obtained by a differential scanning calorimeter (DSC 60, TA-60WS, Shimadzu, Japan) at a heating rate of 10°C/min from 30 to 300°C in an air atmosphere.¹³

Infrared Spectroscopic Studies

Fourier-transformed infrared (FT-IR) spectra were obtained on a Shimadzu, FT-IR 8400 using the KBr disk method (2 mg sample in 200 mg KBr). The scanning range was 450 to 4000 cm^{-1} and the resolution was 1 cm^{-1} .¹⁴

Solubility Studies

The apparent solubility of licofelone, licofelone 1, co-grinding mixtures, and physical mixtures was determined in water at 37°C. For each preparation, an equivalent of 50 mg of drug was added to 50 ml of water in a conical flask with Teflon-lined screw caps. The conical flasks were kept on a shaker incubator maintained at $37 \pm 0.5^\circ\text{C}$ for 24 hours. After shaking, the flasks were kept equilibrated in an incubator at $37 \pm 0.5^\circ\text{C}$ for 12 hours. Then solution was filtered through a 0.45- μm Millipore filter and the filtrate was assayed spectrophotometrically at 280 nm.¹⁵

in vitro Dissolution Rate Studies

Dissolution rates from different solid mixtures were determined in 900 ml of Phosphate buffer solution (pH 7.2) at 37°C with a stirrer rotation speed of 100 RPM using the USP XXIII dissolution rate test apparatus employing a paddle stirrer (Method II). A 5-ml aliquot of dissolution medium was withdrawn at 5, 10, 15, 20, 30, 40, 50, 60, and 90 min with a pipette. The samples were suitably diluted and assayed spectrophotometrically at 280 nm. Each dissolution rate test was repeated 3 times.¹⁶

Statistical Analysis

All the data of solubility studies and *in vitro* dissolution rate studies were analyzed statistically by ANOVA (analysis of variance) test.

Results & Discussion

Characterization OF GG and MGG

Swelling, Water Retention Capacity and Viscosity Measurement

The results of the characterization of the GG and MGG are given in Table 1. The results indicated that the viscosity of MGG was markedly lower when compared to GG. The swelling and water retention capacity of MGG was not reduced significantly rather than that of the GG ($P < 0.05$). Due to the swelling nature of the carrier, the extensive surface of carrier is increased during dissolution, and the dissolution rate of deposited drug is markedly enhanced. Water retention capacity of carrier is the amount of water retained in it that indicates ability of carrier towards hydrophilic nature.

Differential Scanning Calorimetry (DSC)

The DSC thermo grams of licofelone, licofelone 1, GG, and MGG are compared with those for co-grinding mixtures and physical mixtures in Figure 1. The DSC thermo grams of physical mixtures as well as co-grinding mixtures showed peak corresponding to the melting point of pure licofelone, indicating the

absence of chemical interaction between licofelone and GG or MGG.

Infrared Spectroscopic Studies

The FT-IR spectra of licofelone, physical mixtures, and co-grinding mixtures are shown in Figure 2. Physical mixtures and co-grinding mixtures of licofelone with GG or MGG were also found to be identical. The principal IR absorption peaks of licofelone at 1716 cm^{-1} (-C=O carboxyl), $3300\text{-}2500\text{ cm}^{-1}$ (-OH of COOH), 2460 cm^{-1} (-Cl), 2945 cm^{-1} (CH -aliphatic) and 1621 cm^{-1} (C=C -aromatic), were all observed in the spectra of licofelone and solid mixtures with MGG or GG. This spectral observation also thus indicated no interaction between the licofelone and MGG or GG.

Solubility Studies

Solubility data for licofelone, licofelone 1, PM-GG, PM-MGG, CM-GG, and CM-MGG are given in Figure 3. Though the solubility of licofelone from co-grinding mixtures increased significantly, the solubility of licofelone from either of the physical mixtures not increased significantly. ANOVA ($P < 0.05$) performed on the solubility parameter demonstrated that there was a statistically significant difference between the solubility of licofelone from co-grinding mixtures with that of licofelone 1. It was also found that there was no statistically significant difference between the solubility of CM-GG and CM-MGG, indicating that GG and MGG have a similar effect on improving the solubility of licofelone.

in vitro Dissolution Rate Studies

Figure 4 shows that the *in vitro* dissolution profiles of the physical mixtures and the co-grinding mixtures in comparison with pure licofelone and licofelone 1. licofelone 1 exhibited a dissolution profile similar to

that of pure licofelone. It is evident that the rate of dissolution of licofelone and licofelone 1 is very low compared with those of all mixtures tested. Both the physical mixtures had slightly improved dissolution patterns compared with the licofelone drug. PM-MGG, however, showed more improvement in licofelone dissolution, when compared with PM-GG. Though the licofelone dissolution from CM-GG also improved, the increase in dissolution rate of licofelone from CM-MGG was found to be greater. ANOVA ($P < 0.005$) demonstrated that the differences were statistically significant. The rank order values is licofelone / licofelone 1 $<$ PM-GG $<$ PM-MGG $<$ CM-GG $<$ CM-MGG. Due to the hydrophilic nature of the carrier hydrodynamic microenvironment around the particles was changed. During the process of drug dissolution from ordered mixtures of drug and the hydrophilic carrier, when a drug-carrier particle comes in contact with the dissolution fluid, seeping of dissolution medium into the drug-carrier particle takes place, which initiates the formation of a stagnant gel layer of carrier around the particle.

The viscosity of 1% w/v solution of MGG at 28°C is 1645 cps, which is about 3 times lower than that of GG. Hence, the dissolution rate of licofelone is low from physical/co-grinding mixtures containing GG, though the physical state of the drug is identical in the physical/co-grinding mixtures of GG with respect to mixtures of MGG. During the dissolution process, the drug particles that are not agglomerated but disperse rapidly throughout the dissolution medium expose a greater surface area, resulting in rapid drug release. It was observed that GG, which is more viscous than MGG, resulted in the formation of lumps of drug-carrier particles during dissolution, whereas licofelone-MGG particles dispersed rapidly. This factor also contricofeloneted to the significant difference between the dissolution rates of CM-GG and CM-MGG.

Table 1. Characterization Of Guar Gum And Modified Guar Gum

Product	Viscosity* (cps)	Swelling Index* (%)	Water retention capacity* (ml)
GG	4111 ± 52	27.15 ± 2	26.53 ± 3.05
MGG	1542 ± 61	25.45 ± 3	19.50 ± 1.18

*n=3

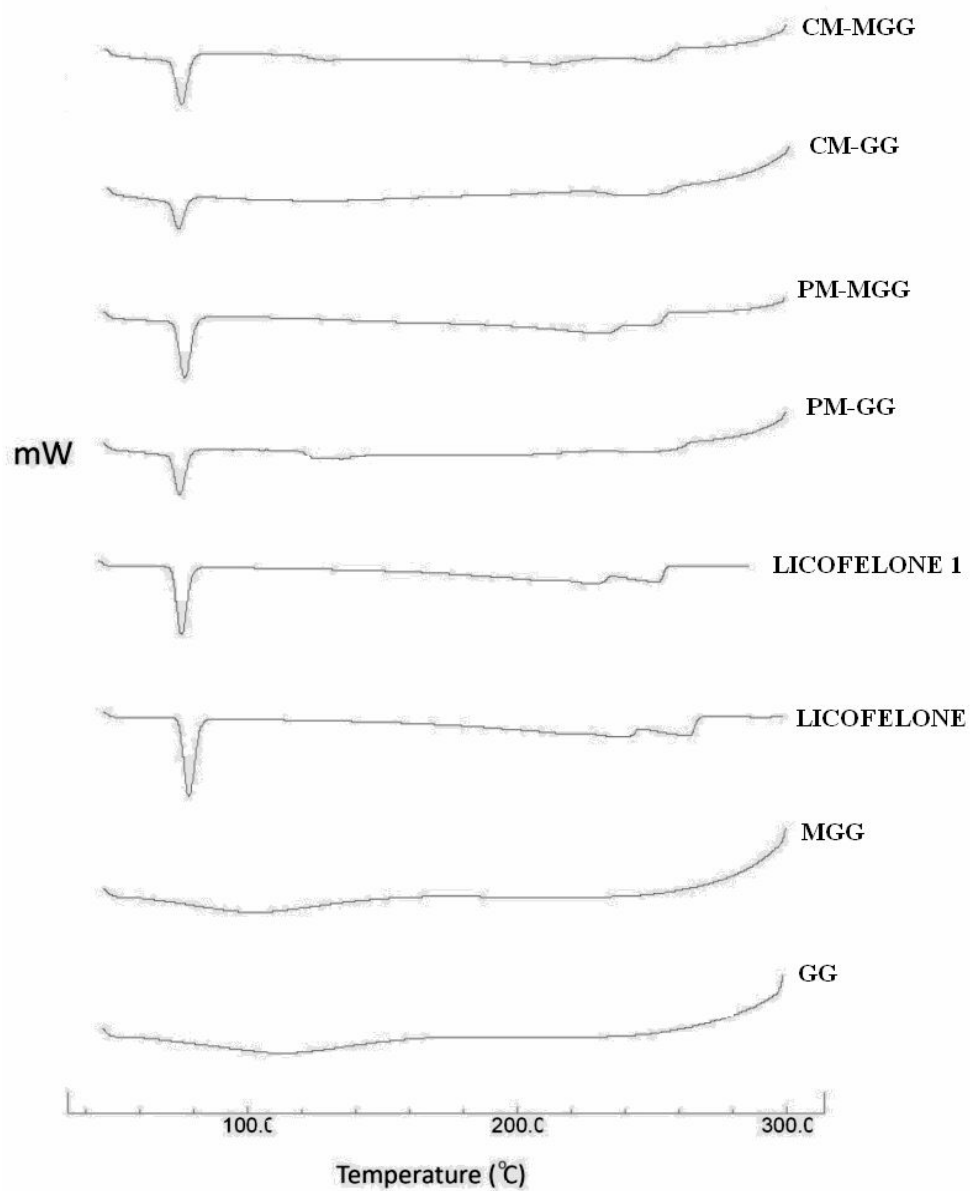


Figure 1. DSC thermograms of physical mixtures and co-grinding mixtures of licofelone and GG or MGG, in comparison with pure licofelone, licofelone1, GG and MGG

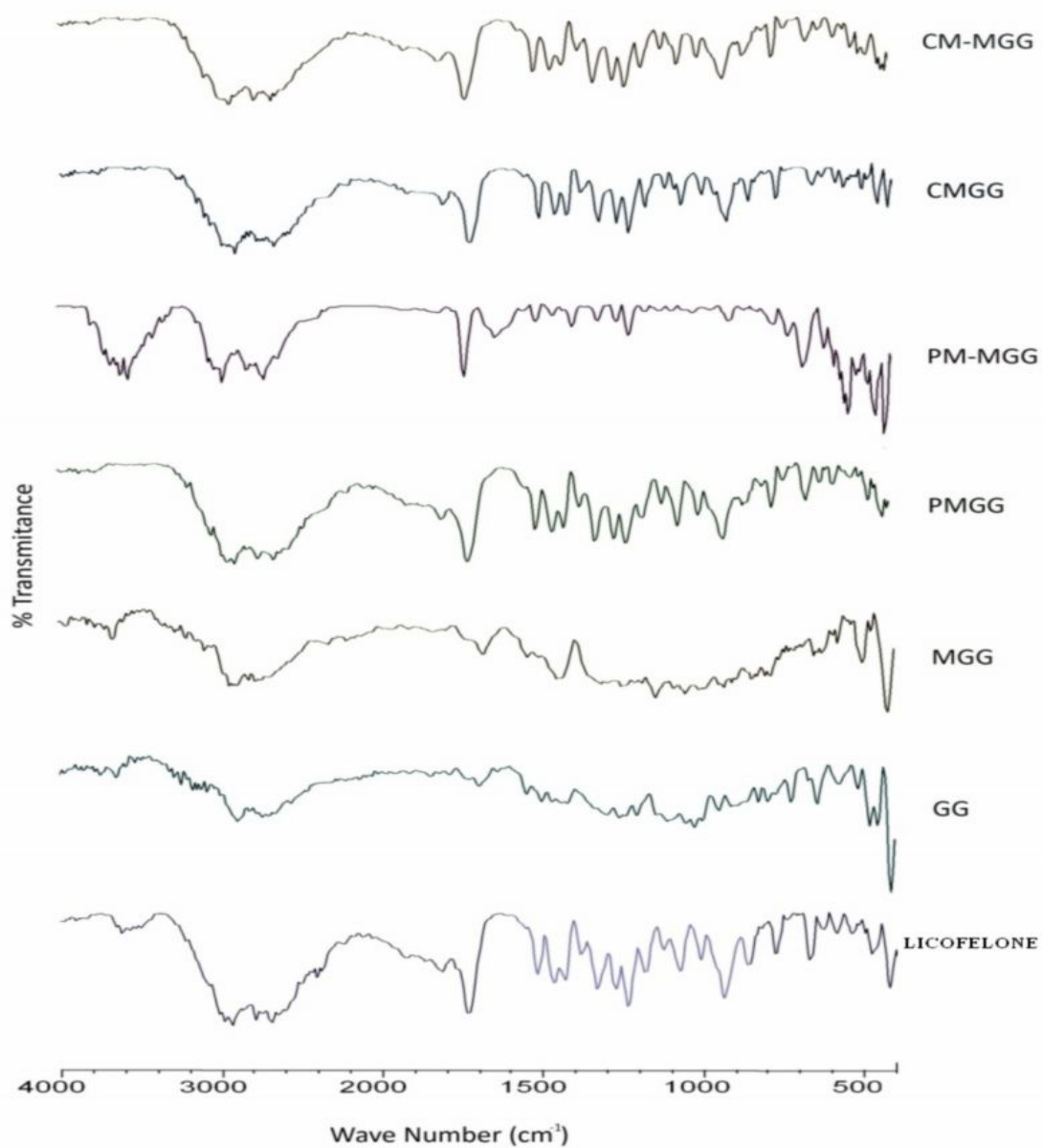


Figure 2. FT-IR spectra of physical mixtures and co-grinding mixtures of licofelone and GG or MGG, in comparison with pure licofelone, GG and MGG.

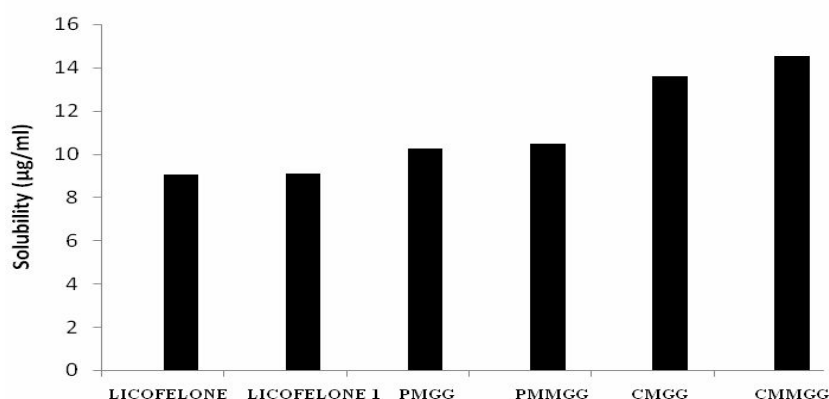


Figure 3. Comparison of solubility values of licofelone from pure licofelone, ground licofelone, physical mixtures and co-grinding mixtures

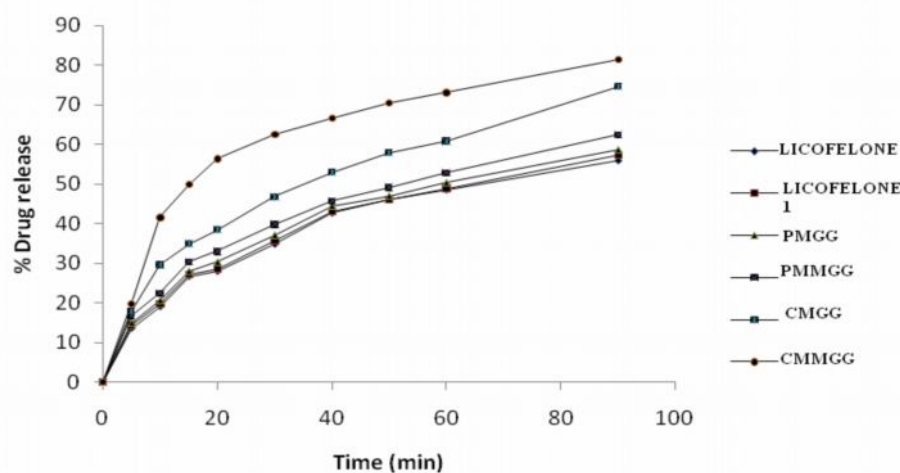


Figure 4. Dissolution profile of licofelone from physical mixtures and co-grinding mixtures of licofelone and GG or comparison with licofelone powder and ground licofelone (licofelone1)

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