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FORMULATION AND EVALUATION OF AL^{+3} -INDUCED GELLAN GUM-*DILLENIA INDICA* L. FRUIT GUM-BLENDED MICROBEADS FOR SUSTAINED DRUG RELEASE

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ABSTRACT: The current communication deals with the development of Al^{3+} -ion induced ionotropically gelled microbeads made of deacetylated gellan gum (GG) and *Dillenia indica* L. fruit gum (DG) blends for sustained release of drugs. Aceclofenac (ACE) was utilized as a model drug candidate in the current study. These GG-DG microbeads of ACE were formulated by ionotropic gelation using $AlCl_3$ as ionotropic cross-linker. In this microbead formulation, various formulation parameters like amount of GG, amount of DG and concentration of $AlCl_3$ were varied and analyzed. These various GG-DG microbeads of ACE demonstrated ACE entrapment efficiency of 24.94 ± 0.32 to 72.76 ± 2.83% and an average micro-bead size of 698.56 ± 19.76 to 955.08 ± 40.62 µm. ACE releasing from various GG-DG microbeads in the *in-vitro* study was found to be sustained over 8 h. Optimized GG-DG microbeads of ACE followed the Korsmeyer-Peppas model (R^2 = 0.9918 to 0.9982) with super case-II transport mechanism of a drug (ACE) releasing. The optimized GG-DG microbeads of ACE (F-O) were also characterized by various instrumental analyses like SEM, FTIR, and DSC analyses.

INTRODUCTION: Gellan gum (GG) is a water-soluble natural gum of anionic in nature, which is obtained from the pure culture fermentation of *Psedomonus eloda*, an aerobic, gram-negative non-pathogenic bacterium [1]. According to the Food and Drug Administration (FDA), it can be safely used as food additive for human consumption [2]. The molecular structure of GG comprises the repeating units of tetrasaccharide, where glucose, glucuronic acid, and rhamnose molecules have occurred in a molar ratio of 2:1:1 [3-4].

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Chemically, GG is acetylated partially, and it interferes in the ion bonding characteristics5. However, the commercial-grade GG is a deacetylated material, which is obtained by means of alkali treatment(s) [2]. Deacetylated GG has excellent iono-tropically gelling capability with the influence of di-/tri-valent metal cations, particularly Ca^{2+} and Al^{3+} ions [6].

This ionotropically gel-formation capability of GG is being exploited to prepare hydrogel beads of GG, and during the past few years, these hydrogel beads are also being investigated as sustained drug-releasing matrices [6-7]. These GG beads have a tendency of losing the mechanical strength over the durable immersion in the aqueous milieu as a result of diffusion and the exchanging of the multivalent cations for the mono-valent ones within the physiological aqueous fluid, which also promotes

premature drug release from ionotropically gelled GG beads in intestinal pH [7]. Although ion-tropically gelled beads made of deacetylated GG only have been examined as matrices for sustained drug release; but the use of a combination of the ionic natural polysaccharides with other bio-compatible polymers is now considered as a familiar approach for improving the desired functional characteristics, such as drug entrapment, stability, swelling, drug-releasing, *etc.* [8-9] Blending of other natural polysaccharides with the deacetylated GG in the formulation of iono-tropically gelled GG beads has been researched to limit the premature drug release in intestinal pH [6-10]. The current work was attempted to develop, characterize and evaluate the ionotropically gelled microbeads made of deacetylated GG and *Dillenia indica* L. fruit gum (DG) blends for sustained release of drugs.

DG is a water-soluble polysaccharide obtained from *Dillenia indica* L. fruit, family: Dilleniaceae [11]. DG was reported as mucoadhesive gelling agents [12]. It was already used as release retardant matrix material in drug delivery [13]. DG was also reported as release retardant polymeric blends with sodium alginate in the formulations of microbeads [14-15]. Though various natural release retardant polymeric blends were investigated to formulate ionotropically gelled GG bead/microparticles for the sustained releasing of drugs, the exploitation of DG as natural release retardant polymeric blends with deacetylated GG is unavailable in the previous literature. Therefore, the development of Al^{3+} -ion induced ionotropically gelled GG-DG microbeads would be an option of sustained drug-releasing multiple-unit matrices over a longer period. ACE, the non-steroidal anti-inflammatory drug (NSAID), was used as a model drug.

ACE [$C_{16}H_{13}C_{l2}NO_4$], 2- [2- [2- [(2, 6-dichlorophenyl) amino] phenyl] acetyl] oxyacetic acid, is given in the treatment of arthritis, osteoarthritis and rheumatoid arthritis [16]. The mechanism of action of ACE is mostly based on the prostaglandin synthesis inhibition as it is a potent inhibitor of cyclo-oxygenase (COX) involving in the generation of prostaglandins [17]. The prolong treatment with ACE is accounted to occur different side effects, such as gastric irritations, ulcers, flatulence, abdominal pain, *etc.* [18-19] ACE is quickly and almost totally absorbed after the administration through the oral route. The plasma elimination half-life of ACE is approximately 4 h [20]. The recommended dose of ACE is 200 mg/daily in the divided doses [21]. Therefore, to decrease the dosing frequencies as well as the occurrences of side effects associated with prolong use of ACE, sustained releasing delivery of ACE for a longer time is essential. Therefore, these desired issues can be achieved by the use of Al^{3+} -ion induced ionotropically gelled GG-DG microbeads of ACE with the increased oral bioavailability and advanced patient compliances. In this formulation of GG-DG microbeads of ACE, various formulation parameters like amount of GG, amount of DG, and concentration of $AlCl_3$ were varied and analyzed.

MATERIALS AND METHODS:

Materials: ACE (Drakt Pharmaceutical Pvt. Ltd., India), deacetylated GG (SRL India Ltd., India), and $AlCl_3$ (Merck Ltd., India) were used in the current work. DG was isolated from ripe *Dillenia indica* L. fruits, which were obtained from Jharpokharia market in September of the year, 2012. All other chemicals were of analytical grade and commercially available.

Isolation of DG: DG was isolated using the previously reported method by Hasnain *et al.*, (2020) with little modifications [12]. Collected *Dellinia indica* L. fruits were washed and chopped into small pieces. 500 g of small pieces of *Dellinia indica* L. fruits were immersed in the double-distilled water and then, heated at 45 ± 1 °C using a water-bath under the occasional stirring until thick slurry of the material was made. This obtained slurry was cooled and then, kept in a refrigerator for an overnight stay with the intention of settling down of the undissolved materials. The clear solution appeared at the upper portion, which was decanted and then centrifuged at 600 rpm for 30 min by a tabletop laboratory centrifuge (Remi Motors, India). The clear supernatant portion was separated through decantation and then was concentrated at 50 ± 1 °C using a water-bath until the volume was decreased to $1/4^{th}$ of the original volume. After that, it was cooled to room temperature. The concentrate was finally poured into the acetone of $1/3^{rd}$ volume with constant stirring by a magnetic stirrer (Remi Motors, India).

The obtained precipitate was then washed repeatedly using acetone and then, dried at 45 ± 1 °C using a tray dryer overnight. The dried product of extracted DG was powdered, passed through a screen of 80-mesh and then, stored in a desiccator until used.

Al^{3+} -ion Induced Ionotropically Gelled GG-DG Microbeads Containing ACE: In brief, aqueous solutions of GG were prepared by heating at 60 ± 1 °C using a magnetic stirrer (Remi Motors, India). On the other hand, aqueous solutions of extracted DG were prepared at room temperature using a magnetic stirrer. The solutions were thoroughly mixed together using a magnetic stirrer with stirring at 600 rpm for 20 min to prepare GG-DG solution mixtures, maintaining 2% w/v polymer concentration in all formulations. Afterward, the required amount of ACE was put into the GG-DG solution mixtures keeping the drug to polymer ratio of 1:2 in all formulations.

The final GG-DG solution containing ACE were homogenized by a table-top homogenizer (Remi Motors, India) at 600 rpm for 20 min. The resultant polymer-drug dispersions were poured drop-wise *via* an 18-gauze needle. The droplets of resultant polymer-drug dispersions were kept in the $AlCl_3$ solutions for 10 min. The wet GG-DG beads were separated by the decantation process, washed for 2 times by double-distilled water, and then, at 45 ± 1 °C using a tray dryer overnight. The prepared dried Al^{3+} -ion induced ionotropically gelled GG-DG microbeads containing ACE were stored in a desiccator for evaluation.

Determination of DEE: GG-DG microbeads of ACE were powdered using clean pestle and mortar. The powdered samples (10 mg) of microbeads were put in a 250 mL volumetric flask. The volume of the volumetric flask containing powdered samples of microbeads was made up to 500 mL by the phosphate buffer (pH 7.4) and left for 24 h at 37 ± 1 °C. After 24 h, the mixture was stirred by a magnetic stirrer (Remi Motors, India) at 500 rpm for 20 min. After the disintegration of the beads, the produced debris was eliminated by filtering using Whatman® filter paper (No. 40). The drug contents in the filtrates were measured by a UV-VIS spectrophotometer (Double-beam, Shimadzu, Japan) at 274.5 nm against the appropriate blank. The DEE (%) of GG-DG microbeads containing ACE was computed using the formula [22]:

DEE (%) = Actual drug content in microbeads / Theoretical drug content in microbeads × 100

Particle Size Determination: Through the optical microscopic methodology, the average particle size of 100 dried GG-DG microbeads containing ACE was determined by an optical microscope (Olympus). A micrometer was calibrated by the stage micrometer, previously.

Scanning Electron Microscopy (SEM) Analyses: The samples were gold coated, and SEM microphotographs were taken by a scanning electron microscope (JEOL Ltd., Japan) at 20 kV of acceleration voltage.

Fourier Transform-infrared (FTIR) Spectroscopy Analyses: The samples were powdered by clean pestle and mortar. The powdered samples were analyzed as the potassium bromide pellets using an FTIR spectroscope (Shimadzu, Japan). The potassium bromide pellets were individually placed in the sample holder of the FTIR spectroscope. The FTIR spectral scanning was obtained in-between 4000-400 cm^{-1} wavelength region with 1 cm/sec scan speed.

Differential Scanning Calorimetry (DSC): For DSC analyses, the samples were made moisture-free. The samples to be analyzed (7 mg) were positioned a platinum crucible-aluminum pan in the hermetically sealed condition, where ∞-alumina powder was utilized as a reference. The DSC thermograms of samples were obtained using a differential scanning calorimeter (Perkin Elmer® Instrument, Japan) at 10 °C/min of heating rate under the constant flow of N_2 gas with the 150 mL/min of flow rate.

***In-vitro* Drug Release Study:** The ACE release from various Al^{3+} -ion induced ionotropically gelled GG-DG microbeads was studied in a dissolution apparatus of basket-type (USP/BP/IP dissolution apparatus, Campbell Electronics, India) at 37 ± 0.5 °C under 50 rpm speed. To avoid the escaping of the beads, the basket of the dissolution apparatus was covered with a nylon cloth of 100 mesh. GG-DG microbeads equivalent to 100 mg ACE was added to 900 ml 0.1 N HCl (pH 1.2). The

in-vitro drug release was studied in the 0.1 N HCl (pH 1.2) for the initial 2 h, and subsequently, continued in the phosphate buffer (pH 7.4) for the next 6 h, a total of 8 h of release. At the regular time intervals, 5 ml aliquots were withdrawn from the dissolution apparatus, and immediately, the same amount of fresh dissolution medium was replaced. The withdrawn aliquots were filtered, and the drug contents were measured using a UV-VIS spectrophotometer (Shimadzu, Japan) at 271.5 nm.

Analysis of *In-vitro* Drug Release Kinetics and Mechanism: The *in-vitro* drug release data of GG-DG microbeads containing ACE were kinetically assessed by important mathematical models and the accuracy (prediction ability) of these mathematical models was compared by the values of squared correlation coefficient (R^2) [23-24].

Zero-order model: $Q = k0 . t + Q0$

First-order model: $Q = Q0\ e\ k1. t$

Higuchi model: $Q = kh . t0.5$

Korsmeyer-Peppas model: $Q = kk\text{-}p . tn$

Where Q is the cumulative amount of drug released in time t, Q0 is the start value of Q, k0, k1, kh, and Kk-p are the rate constants for zero-order, first-order, Higuchi, and Koresmeyer-Peppas models, and n is the release exponent, suggesting drug release mechanisms.

In case of the spherically shaped matrices, when n is ≤ 0.43, it is the Fickian (diffusion controlled) mechanism. The n value in-between 0.43-0.85 is defined as the non-Fickian (anomalous transport) mechanism. When, n is ≥ 0.85, it is the case-II transport (relaxation controlled) mechanism [25-26].

Statistical Analysis: All other measured data analyzed by the simple statistics by MedCalc software, version 11.6.1.0 (trial version).

RESULTS AND DISCUSSION:

Preparation of Al^{3+} -ion Induced Ionotropically Gelled GG-DG Microbeads Containing ACE: The gelation of deacetylated GG with the influence of di-/tri-valent metal cations is called ionotropic-gelation of GG and the mechanism of this ionotropic gelation of deacetylated GG entails the arrangement of the double helical junction zones subsequently the aggregation of the double helical segments to structure 3-dimensional networking by the complexation with di-/tri-valent metal cations and the hydrogen bonding with the water molecules [27-29]. In the previous literature, blending of other plant polysaccharides with deacetylated GG in the formulation of ionotropically gelled GG beads have been reported for improving the preferred functional characteristics, such as drug encapsulations, drug releases, swelling, stability, *etc.* [6-10]

Most of these plant polysaccharide blended GG beads were developed using $CaCl_2$ as ionotropic cross-linker. It has also been accounted that the rate of cross-linking for tri-valent Al^{+3} ions is faster than di-valent Ca^{+2} ions due to higher valency[2]. Moreover, the GG beads cross-linked with Al^{+3} cations are reported to encapsulate a higher percentage of drug retard the release of an encapsulated drug over a longer duration in the alkaline pH than those of the GG beads cross-linked with Ca^{+2} ions[2]. This is why in this investigation, Al^{+3} ions instead of Ca^{+2} ions for the preparation of ionotropically gelled GG-DG microbeads containing ACE. When dispersion mixtures of GG, DG, and ACE were added drop-wise into the counter ion solutions, which contains Al^{+3} ions, spherically shaped white colored ionotropically gelled GG-DG microbeads containing ACE were shaped immediately.

DEE: The DEE (%) of Al^{3+}-ion induced ionotropically gelled GG-DG microbeads containing ACE ranged, 24.94 ± 0.32 to 72.76 ± 2.83% **Table 1**. The investigated formulation parameters, amount of GG, amount of DG, and concentration of $AlCl_3$ significantly controlled the DEE (%) ($p < 0.05$). The ACE encapsulations in the GG-DG microbeads of ACE were found improved with the escalating amounts of polymers used (*i.e.*, GG and DG) and decreasing concentration of $AlCl_3$. The increment of DEE in these beads could be due to the increment in the polymer blend solution's viscosity by raising the amounts of polymers addition in the solutions of polymer blends, which might have been disallowed the drug leaching from the formed GG-DG microbeads to the solutions containing cross-linker [7]. The decreasing drug encapsulations in these microbeads containing ACE with the increment of $AlCl_3$ concentrations may be accredited by the reality,

where the water content might become out from the polymer-matrix as the ionotropic gelation proceeds by the Al^{3+} -ions. The coming out of water contents might produce the convective loss of the drug contents in this Al^{3+} -ion induced ionotropically gelled GG-DG microbeads during preparation due to higher degrees of cross-linking.

TABLE 1: FORMULATION PARAMETERS OF DIFFERENT AL^{3+} -ION INDUCED IONOTROPICALLY GELLED GG-DG MICROBEADS CONTAINING ACE WITH DEE (%) AND AVERAGE MICROBEADS DIAMETER (MM) RESULTS

Code	Formulation parameters				Average microbeads diameter (µm)c
	Amount of GG (mg)	Amount of DG (mg)	Concentration of $AlCl_3$ (%)	DEE (%)a, b	
F-1	280	50	5	33.92 ± 1.05	861.73 ± 27.28
F-2	280	50	3	48.45 ± 1.51	883.34 ± 32.40
F-3	280	0	5	26.45 ± 0.53	742.09 ± 20.18
F-4	280	0	3	35.03 ± 1.03	781.24 ± 23.82
F-5	250	50	5	27.85 ± 0.42	790.79 ± 23.93
F-6	250	50	3	44.98 ± 1.36	843.26 ± 28.37
F-7	250	0	5	24.94 ± 0.32	698.56 ± 19.76
F-8	250	0	3	36.72 ± 0.93	767.18 ± 22.54
F-O	280	100	2	72.76 ± 2.83	955.08 ± 40.62

[a]DEE (%) = drug encapsulation efficiency (%), [b](Mean ± S.D.; n = 3), [c]Mean ± S.D.; n = 100.

Microbead Size: The average particle size of Al^{3+} -ion induced ionotropically gelled GG-DG microbeads containing ACE was within the range of 698.56 ± 19.76 to 955.08 ± 40.62 µm **Table 1**. The increasing size was noticed with the more addition of GG and DG amounts and decreasing of $AlCl_3$ concentrations in the solutions employed for ionotropic cross-linking. Increasing microbead size with increasing addition of polymer amounts in blend solutions could be elucidated on the basis of the concept of hydrodynamic viscosity [6]. The viscosity enhancement of the polymer blend solutions with the addition of polymers (*i.e.*, GG and DG) in increasing ratio might form larger droplets of polymer-blend solutions during passing through the needle to the solutions employed for ionotropic cross-linking containing Ca^{2+} ions. Also, decreasing of GG-DG micro-bead size was observed with the use of increasing concentrated $CaCl_2$ solutions and could be attributable to the contraction of polymer gel matrix by the elevated extent of ionotropic cross-linking by more concentrated cross-linking ions. This is in agreement with the earlier reports [7-8, 30-31].

SEM Analyses: SEM photograph of optimized Al^{3+}-ion induced ionotropically gelled GG-DG microbeads containing ACE (F-O) is presented in **Fig. 1**, which indicates the surface morphology characteristics of these newly formulated microbeads. The SEM microphotograph of the GG-DG microbeads at the magnification of 181 x demonstrated that these microbeads were irregularly shaped with rough and corrugated surface morphology and without any agglomeration. In addition, some wrinkles were also observed on the microbead surface, which might be occurred due to some degree of collapsing of the developed iono-tropically gelled network made of GG-DG during the drying of these microbeads [32].

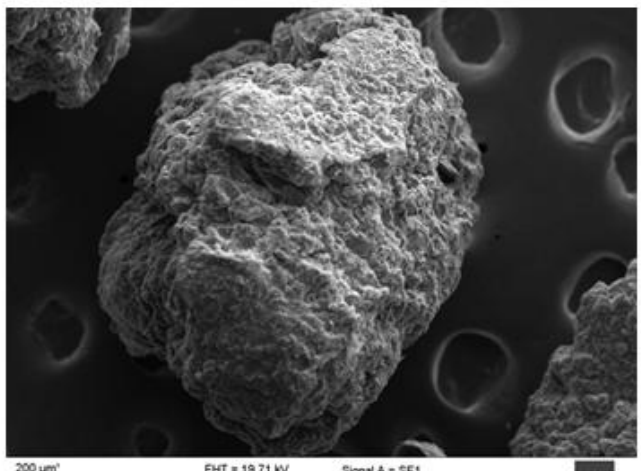

FIG. 1: SEM PHOTOGRAPH OF OPTIMIZED AL^{3+} -ION INDUCED IONOTROPICALLY GELLED GG-DG MICROBEADS CONTAINING ACE (F-O)

FTIR Spectroscopy Analyses: The FTIR spectra analyses of GG, DG, GG-DG microbeads without ACE, GG-DG microbeads of ACE (F-O), and pure ACE are presented in **Fig. 2**. The FTIR spectrum of GG revealed a characteristic peak at 3630.8 cm^{-1} because of the stretching of –OH groups, band at

2920–3300 cm^{-1} owing to C-H stretching, peak at 1663.5 cm^{-1} indicating stretching of C=O, peak at 1403.6 cm^{-1} for methyl –C-H bonding and peak at 889.7 cm^{-1} for -C-O stretching of alkyl ether group. The FTIR spectrum of DG demonstrated characteristic peaks at 3622.8 cm^{-1} owing to stretching of –OH group, 1735.2 cm^{-1} and 1514.1 cm^{-1} demonstrating cyclic ketones and aromatic – NO_2, respectively. The FTIR spectrum of optimized GG-DG microbeads without ACE confirmed almost all the characteristic peaks/bands of both GG and DG, devoid of any significant deviation. The FTIR spectra of pure ACE demonstrated the characteristic band at 3317.6 cm^{-1} for secondary N-H rocking vibrations, characteristic peaks at 3029.6 for aromatic -C-H stretching vibration, and at 2939.8 cm^{-1} owing to stretching vibrations of aliphatic -C-H, a sharp band at 1770.7 cm^{-1} for C=O stretching of carboxylic acid, a band at 1717 cm^{-1} for C=O stretching vibration, and a sharp peak at 717.5 cm^{-1} for the stretching vibration of 1, 2 di-substituted C-Cl. The FTIR spectra of the formulated GG-DG microbeads of ACE (F-O), different characteristic peaks/bands of GG, DG, and ACE appeared without any shifting/alteration significantly. Thus, it can be said that the optimized GG-DG microbeads of ACE (F-O) had retained the significant qualities of ACE. This result suggests the absence of any interaction between ACE and the polymers used as blends in the GG-DG microbeads preparation (*i.e.*, GG and DG), indicating that ACE maintained its characteristics after the formulation of GG-DG microbeads containing ACE (F-O) through Al^{3+} -ion induced ionotropic gelation.

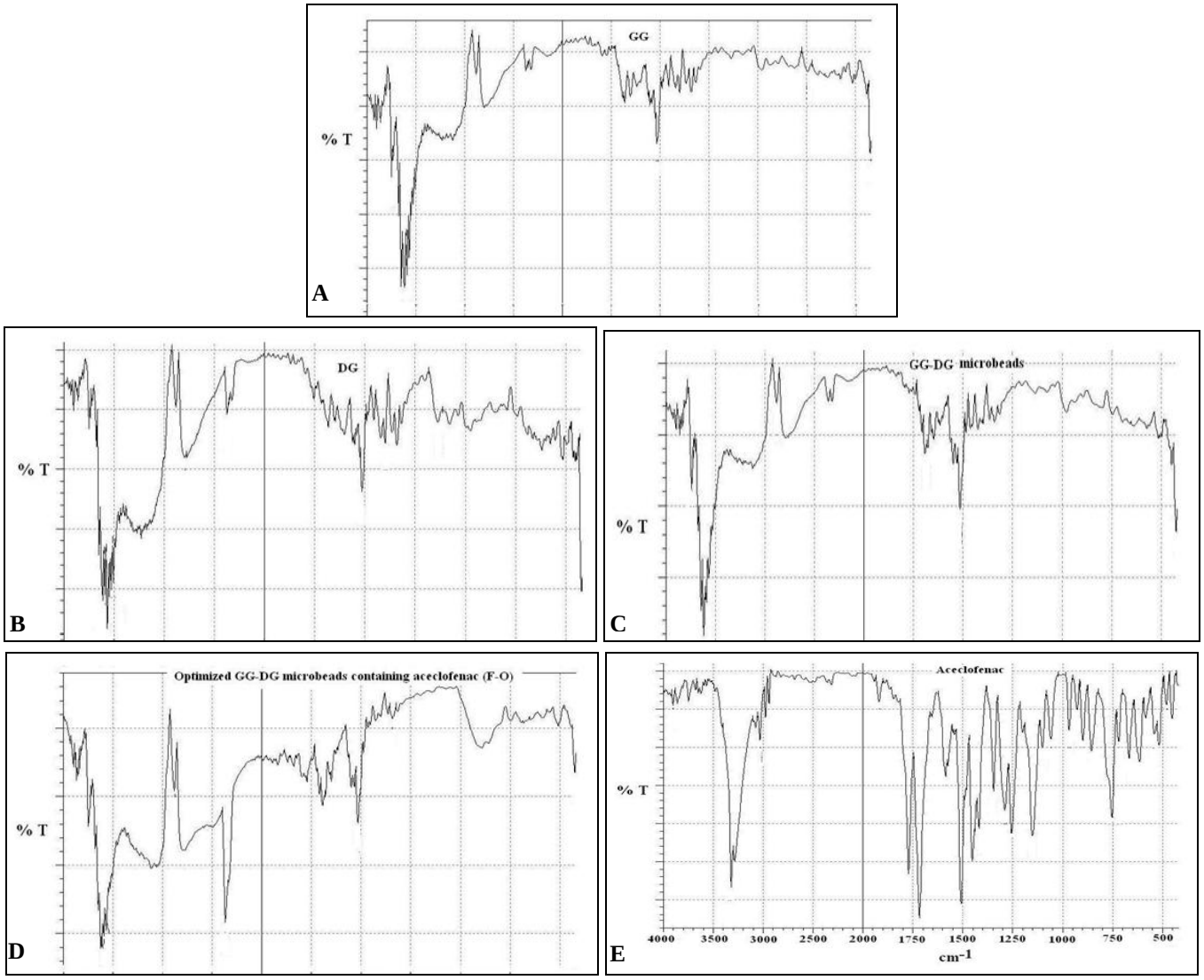

FIG. 2: FTIR SPECTRA ANALYSES OF GG (A), DG (B), GG-DG MICROBEADS WITHOUT ACE (C), GG-DG MICROBEADS CONTAINING ACE (F-O) (D) AND PURE ACE (E)

DSC Analysis: DSC thermograms of pure ACE and optimized GG-DG microbeads containing ACE (F-O) are presented in **Fig. 3**. These DSC thermograms indicate the physical states of the drug (here ACE) in pure ACE and in optimized GG-DG microbeads containing ACE (F-O). The DSC thermogram of pure ACE showed a sharp characteristic endothermic peak at 153.53 ºC **Fig. 3A** demonstrating the transition melting point temperature of ACE. In the DSC thermogram of optimized GG-DG microbeads containing ACE (F-O) **Fig. 3B**, a noticeable weaker endothermic peak was found at 130.06 ºC demonstrating the reasonably amorphous dispersion of ACE (than the state of ACE in the pure form) within the GG-DG microbead-matrices. The shifting of the sharp endothermic peak (seen in the thermogram of pure ACE) to the wider endothermic peak at the lesser temperature could be for the conversion of a comparatively amorphous form of ACE after the encapsulation of ACE within these GG-DG microbeads through Al^{3+} -ion induced ionotropic gelation technique.

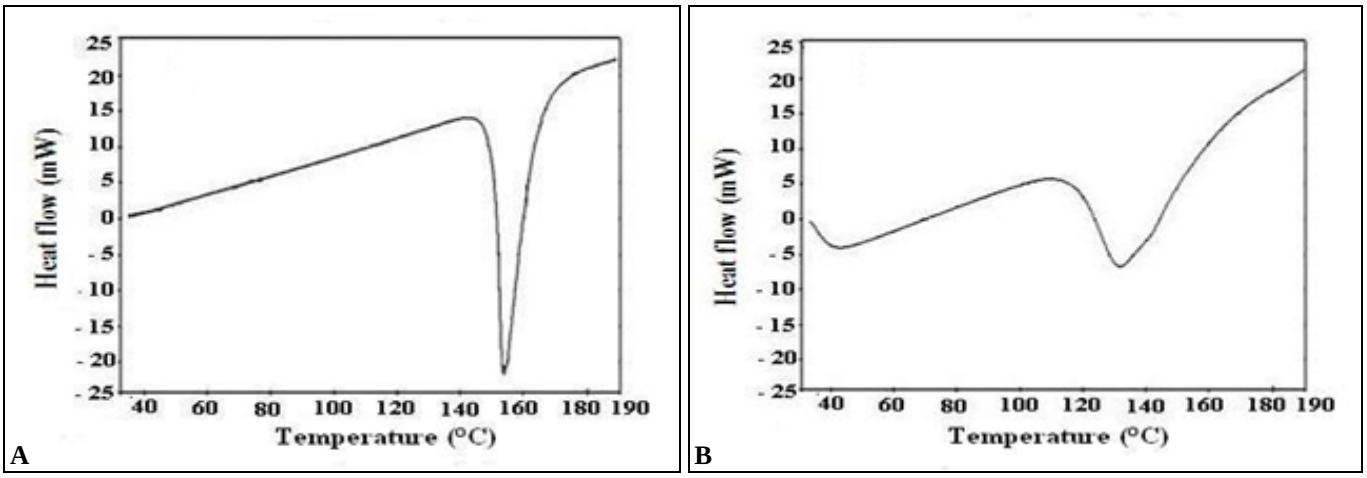

FIG. 3: DSC THERMOGRAMS OF PURE ACE AND GG-DG MICROBEADS CONTAINING ACE (F-O)

***In-vitro* Drug Release:** All these formulated Al^{3+}-ion induced ionotropically gelled GG-DG microbeads containing ACE (F-1 to F-8, and F-O) showed prolonged *in-vitro* ACE releasing over a period of 8 h **Fig. 4**. ACE releasing from GG-DG microbeads was comparatively slower in 0.1 N HCl (acidic dissolution medium; pH 1.2) and after that, the faster ACE release was observed in phosphate buffer (alkaline dissolution medium; pH 7.4). This phenomenon could be occurred due to the fact that these ionotropically gelled GG-based microbeads might swell rapidly in the alkaline medium as compared to that in the acidic medium, which might led to a comparatively increment of the drug-releasing in the alkaline release medium. In the alkaline release medium, a larger swelling force might be produced by the electrostatical repulsion effect in-between the ionized –COOH groups of the GG-backbone [6]. In fact, the gel-structure of these ionotropically gelled GG-based microbeads might become loose and soluble when exposed to in the alkaline natured phosphate buffer (pH 7.4), because the Al^{3+}ions involved in the ionotropically-gelled GG-based network could not only be displaced by the Na^{+} ions but also be sequestered by phosphate ions present in phosphate buffer (pH 7.4). The maximum amount of released ACE from these GG-DG microbeads at the preliminary stage of the *in-vitro* drug release study could probably be due to the surface adhered ACE crystals. Retardation of ACE release from this Al^{3+}-ion induced ionotropically gelled GG-DG microbeads were observed with increasing amounts of GG and DG. With the increasing amounts of GG and DG in the GG-DG microbeads, the hydrophilic property of these polysaccharide-blends (*i.e.,* GG-DG blends) in the microbeads formulation was increased. Thus, GG-DG blend microbeads could combine better with the water molecules, which might produce the viscous gel-structure on the micro-bead surface. This viscous gel might blockade the pores on the surfaces of these microbeads of ACE to produce the sustained the drug-releasing. Moreover, the retardation of ACE release from these GG-DG microbeads prepared with a higher concentration of $AlCl_3$ (*i.e.,* cross-linker) could be due to the fact

that the free volume of matrix decreases and the hindering movements of the solute through the GG-DG microbead matrix at higher degree of cross-linking.

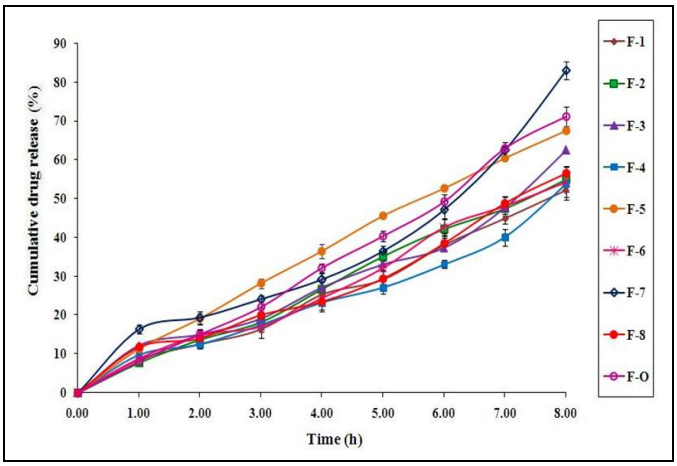

FIG. 4: *IN-VITRO* ACE RELEASE FROM VARIOUS AL^{3+} -ION INDUCED IONOTROPICALLY GELLED GG-DG MICROBEADS CONTAINING ACE (F-1 TO F-8 AND F-O)

The ACE releasing (*in-vitro*) data from Al^{3+} -ion induced ionotropically gelled GG-DG microbeads of ACE (F-1 to F-8 and F-O) were kinetically analyzed by using important mathematical models. The result of the curve fitting into various mathematical models is given in **Table 2**. When respective correlation coefficients were compared, it was found that the *in-vitro* ACE release from F-1, F-2, F-5, F-6, and F-O microbeads followed the zero-order model (R^2 = 0.9844 to 0.9986). Furthermore, in the case of F-2, F-5, and F-O microbeads, the Korsmeyer-Peppas model (R^2 = 0.9918 to 0.9982) was noticed to be closer to the best-fit zero-order model. Other microbeads (F-3, F-4, F-7 and F-8) was noticed to follow the first-order model (R^2 = 0.9906 to 0.9947). The release exponent (n) values computed from the *in-vitro* drug-releasing results of Al^{3+} -ion induced ionotropically gelled GG-DG microbeads containing ACE (F-1 to F-8, and F-O) ranged from 0.7571 to 1.0570. F-1, F-2, F-5, F-6, and F-O microbeads, which were prepared using GG-DG polymer-blends, exhibited 'n' values range within 0.8752 to 1.0570, demonstrating the super case-II transport mechanism of the drug (ACE) releasing. The super case-II transport mechanism demonstrates that the drug-releasing from these developed polymeric microbeads could be controlled by the occurrence of swelling as well as relaxation of the ionotropically gelled matrices [33]. This phenomenon could be attributed to the dissolution, enlargement and/or relaxation of the polymeric chains of the GG-DG micro-bead matrix. On the other hand, F-3, F-4, F-7 and F-8 microbeads, which were prepared using GG only, exhibited 'n' values range less than 0.85 (between 0.7571 to 0.8062) demonstrating the non-Fickian releasing (anomalous transport) mechanism, which is an indication of diffusion as well as swelling controlled releasing of the encapsulated drug from these microbeads [34].

TABLE 2: RESULTS OF CURVE FITTING OF THE *IN-VITRO* ACE RELEASE DATA FROM AL3+-ION INDUCED IONOTROPICALLY GELLED GG-DG MICROBEADS CONTAINING ACE

Models		Formulation code								
		F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-O
Zero order	R^2	0.9880	0.9956	0.9517	0.9558	0.9986	0.9844	0.9072	0.9627	0.9940
First order	R^2	0.9740	0.9452	0.9921	0.9906	0.9293	0.9686	0.9925	0.9947	0.9514
Higuchi	R^2	0.6745	0.6659	0.6829	0.6789	0.7678	0.6765	0.6116	0.6933	0.5888
Korsmeyer-Peppas	R^2	0.9703	0.9918	0.9295	0.9466	0.9982	0.9700	0.8704	0.9230	0.9929
	n	0.9017	0.9669	0.7807	0.8062	0.8752	0.8994	0.7571	0.7740	1.0570

R^2 = squared correlation coefficients, n = diffusional exponent.

CONCLUSION: In the present work, Al^{3+} -ion induced ionotropically gelled GG-DG microbeads containing ACE was successfully developed by the ionotropic gelation. These various GG-DG microbeads of ACE demonstrated ACE entrapment efficiency of 24.94 ± 0.32 to 72.76 ± 2.83 % and average microbead size of 698.56 ± 19.76 to 955.08 ± 40.62 µm. These GG-DG microbeads containing ACE demonstrated sustained *in-vitro* ACE releasing pattern over 8 h, which could probably be valuable in terms of the advanced patient compliances with the advantage of decreased dosing intervals. Hence, Al^{3+}-ion induced ionotropically gelled GG-DG microbeads containing ACE can be employed as prospective alternative carrier-matrices for the sustained

releasing of ACE over a longer time. On the whole, this work presented an easy and also, economical approach to develop Al^{3+}-ion induced ionotropically gelled GG-DG microbeads for sustained drug release. These GG-DG microbeads containing ACE also can be advantageous for the sustained releasing of other drugs, which need intestinal drug delivery.

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