

# Preparation, Characterization and Evaluation of Chitosan–Gum Arabic Coacervates as Excipient in Fast Dissolving/Disintegrating Dosage Form

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*Preparation, Characterization and Evaluation of Chitosan–Gum Arabic Coacervates as Excipient in fast dissolving/disintegrating dosage form*

## Summary

The aim of present research was to synthesize coacervates of two natural polymers viz. chitosan and gum Arabic, and further coacervates was characterized and evaluated as an excipient in the fast disintegrating dosage form for treatment of chronic epileptic attack. Coacervates were synthesized by mixing of separately prepared solution of chitosan and gum Arabic at controlled temperature. After vacuum drying, coacervates were used as pharmaceutical excipient; moreover they were used in varying ratios to formulate six batches of tablets and evaluated for pre-compression and post-compression parameters. The physicochemical evaluation results demonstrate that coacervates had good potential to be used as pharmaceutical excipient. Thus, coacervates may have wide range of applications as polymer in different dosage form. The fast disintegrating tablet dosage forms can be formulated using such coacervates on commercial scale.

**Key Words:** chitosan, gum Arabic, coacervates, fast dissolving/ disintegrating drug delivery system, Phenytoin sodium.

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*Çabuk çözünen/dağılan dozaj şeklinde eksipiyen olarak kullanılmak üzere kitosan-arap zamkı koaservatlarının hazırlanması, karakterizasyonu ve değerlendirilmesi*

## Özet

Bu çalışmada, doğal polimer olan kitosan ve arap zamkının koaservatlarını hazırlamak, ve bu koaservatların kronik epileptik nöbetlerin tedavisinde kullanılacak hızlı dağılan tabletler için eksipiyen olarak incelenmesi amaçlanmıştır. Koaservatlar ayrı ayrı hazırlanan kitosan ve arap zamkı çözeltilerinin kontrollü sıcaklıkta karıştırılmasıyla hazırlanmıştır. Vakumda kurutma yapıldıktan sonra, koaservatlar değişik oranlarda kullanılarak altı farklı tablet serisi hazırlanmış, ve basım öncesi ve sonra parametreler incelenmiştir. Fizikokimyasal değerlendirmeler sonucunda uygun eksipiyen olduğunu gösteren sonuçlar elde edilmiştir. Koaservatların farklı dozaj şekillerinde uygun bir polimer olarak kullanılabileceği gösterilmiştir. Bu koaservatların kullanımı ile hızlı dağılan tabletler ticari boyutta üretilebileceği düşünülmektedir.

**Anahtar Kelimeler:** Kitosan, arap zamkı, koaservatlar, hızlı çözünen/dağılan ilaç taşıyıcı sistemler, fenitoin sodyum

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## INTRODUCTION

Coacervates are generally formed by physical non-ionic interaction between two different polymer solutions (1,2). This type of new polymer exhibits unique physical and chemical properties because of physical interactions of one ionic and other anionic polymer. Many studies have been done to use composites of chitosan and polyanions for pharmaceutical applications (3,4). Chitosan, poly-b-(1-4)-2-amino-2-deoxy- D-glucose, is a naturally occurring cationic polysaccharide derived from the N-deacetylation of chitin. At acidic pH ranges, the ionizable amino groups in chitosan molecules are protonated (5,6). The formation and the properties of coacervates depend on various factors including, physicochemical interactions, charge density and concentration of both polymers; it also depends upon proportion of charges, molecular weight of the macromolecules and conditions of synthesis (7,8,9,10). Most of the natural polysaccharides are anionic in nature such as gum Arabic, alginate, xanthan gum, guar gum and gellan gums etc. Gum Arabic an anionic polymer is a natural polysaccharide derived from exudates of *Acacia senegal* and *Acacia seyal* trees (11). Any improvement in properties (such as hydrophilicity) is expected to be solely based on interaction between two different natural polymers. Espinosa-Andrews et al; already studied chitosan- gum Arabic coacervates and quantified the amounts of polysaccharides in soluble phase and insoluble phase (coacervates). They used high pressure liquid chromatography (HPLC) technique to quantify monosaccharides produced after acidic hydrolysis in soluble phase (12). Tapia et al, has been formulated prolonged release formulations using mixtures of polyelectrolyte complexes of chitosan-carrageenan and chitosan-alginate (13). Espinosa-Andrews et al, prepared chitosan-gum Arabic coacervates at different pH and further evaluated micro- structural and rheological characteristics of coacervates. They found that coacervates were formed due to the interaction of the functional groups of both macromolecules ( $-NH_3^+$  and  $-COO^-$ ), using Fourier Transform Infrared Spectroscopy (FT-IR) (14). This paper attempts to investigate the feasibility of chitosan-gum Arabic coacervates, as excipient in the treatment of chronic epileptic attack

using Phenytoin sodium as model drug. Phenytoin sodium is commonly used anticonvulsant which is useful in the treatment of status epileptics of the grand mal seizures type.

## MATERIALS AND METHODS

### Materials

Drug Phenytoin sodium was purchased from Alchem Laboratories, Baddi, India. Gum Arabic, Sodium carboxymethyl cellulose and magnesium stearate were procured from CDH Laboratory reagent, "central drug house" (P) Ltd, New Delhi, India. Chitosan (Medium molecular weight, viscosity 200.000 cps) was purchased from Sigma-Aldrich, Spruce Street, St. Louis. All materials were of pharmaceutical grade and used as supplied without further purification.

### Preparation of chitosan- gum Arabic composite

Chitosan gel (5%) was prepared using 2% acetic acid solution. Continuous agitation and heating makes a gel formation at temperature about 45°C. Temperature was further increased up to 70°C with continuous stirring. Gum Arabic was added in deionised water to form homogeneous solution of 5% (w/v). Temperature of gum solution was increased slowly up to 60°C.

To prepare composites, equal proportion of both solutions was mixed for 30min with continuous stirring and temperature of mixture was reduced (25-35min) within the range of room temperature (30-35°C). This solution was further dried under vacuum. Dried composites was powdered and passed through sieve #20, and stored in airtight container for further study.

### Characterization of chitosan-gum Arabic coacervates

#### Infrared study of excipients

Infrared study was carried out with aim to investigate either any interactions have taken place between excipient and drug or not. An infrared spectrum of drug, sodium alginate and gum Arabic is characteristics for it and if any change in peak will observe in the mixture of coacervates and drug, shows interaction between excipients.

### **Surface morphology of composite particles**

The surface characteristics of coacervates were observed by scanning electron microscopy (Leo 435 VP, Carl Zeiss NTS GmbH, Oberkochen, Germany). Dried powdered coacervates were passed through sieve #20 and coated with gold using a sputter coater (Agar sputter coater, Agar Scientific, Stansted, UK) under high vacuum and high voltage. The samples were imaged using high energy electron beam.

### **Estimation of Particle Size**

Particle size of prepared coacervates was measured by an optical microscope fitted with an ocular and stage micrometer and particle size distribution was calculated. In this measurement 50 particles in 5 different fields were examined.

### **Bulk density**

Apparent bulk density (g/mL) was determined by placing pre-sieved bulk powder blend into a graduated cylinder via a funnel and measuring the volume and weight of powder blend (15,17).

$$\text{Bulk density} = \frac{\text{weight of powder blend}}{\text{unsettled apparent volume}}$$

### **Tapped density**

It was determined by placing a graduated cylinder, containing a known mass of powder on mechanical tapping apparatus, which was operated for fixed number of taps (around 50). Using the weight of powder in a cylinder and its tapped volume, the tapped density was computed, (15,17):

$$\text{Tapped density} = \frac{\text{weight of powder blend}}{\text{tapped volume of powder blend}}$$

### **Carr's index**

It is an important parameter to study compressibility behaviour of composites. Carr's index was calculated, from the results of bulk density and tapped density (15,16,17).

$$\text{Carr's index} = \frac{\text{tapped density} - \text{bulk density}}{\text{tapped density}} \times 100$$

### **Bulkiness**

It is reciprocal of bulk density and calculated as (15,17):

$$\text{Bulkiness} = \frac{1}{\text{bulk density}}$$

### **Angle of repose**

Angle of repose of powdered coacervates was determined using official methods (15,17).

### **Preparation of complex based tablets:**

#### **Granulation**

In present research wet granulation technique was used to prepare matrix tablet. Dose of drug (Phenytoin sodium) was taken 30 mg for each tablet and was added accordingly. According to table 1, all the ingredients were mixed physically for 25 min, using a mortar pestle. Using appropriate amount of distilled water, powdered mixture was converted into wet mass. Wet mass was passed through 20 mesh- sieve to obtain granules; further granules were dried at 45°C until granules were completely dried.

#### **Preparation of tablets**

Equivalent to 500 mg (tablet weight), granules were taken per tablet and then compressed using Cadmach punching machine (16 Station, Type: CMD3-16/MT, Cadmach Machinery Co. Pvt. Ltd. Ahmadabad, India) with 12 mm diameter flat faced tolling. Tablets were compressed at compression force of 2 N for 10 s (18).

### **Evaluation of complex based tablets:**

#### **Evaluation for weight variation**

Test was carried out according to the European Pharmacopoeia. Twenty tablets were randomly selected from each batch and the mean of tablet weights was calculated. Results are presented as mean value with standard deviation (15,18).

#### **Tablet thickness testing**

The thickness of the matrix tablets (20 tablets of each batch) was determined using vernier callipers (Mitutoyo Dial Thickness Gauge, Mitutoyo, Japan)

and the results were expressed as mean values of 10 determinations, with standard deviations (15,18).

#### **Evaluation for tablet hardness**

Hardness of all batches (20 tablets of each batch) was determined using Digital Force Gauge (Model: EL=500N, Electrolab). The test was carried out in triplicate for all batches as per USP XXIV monograph for uncoated tablets. The tablet hardness was expressed in Newton (N) and mean with standard deviation of tablet hardness was calculated (15,18).

#### **Friability measurement**

Twenty tablets were selected randomly from each batch, were used to study friability (Friabilator-Erweka type, GmbH, Germany) (15,18).

#### **Drug content**

The 20 tablets were powdered, and 30 mg equivalent weight of Phenytoin sodium in tablet powder was accurately weighted and transferred into a 100 ml volumetric flask. Initially, 10 ml of phosphate buffer (pH6.8) was added and shaken for 10 min. Then, the volume was made up to 100 ml with buffer. Subsequently, the solution in volumetric flask was filtered, and 1 ml of the filtrate was diluted and analysed at 252 nm using UV-visible spectrophotometer (Shimadzu UV-2450, Japan). The drug content of the each sample was estimated from standard curve (15,18).

#### **In vitro disintegration time**

Tablets of all batches were selected and evaluated for disintegration time in distilled water kept at  $37 \pm 0.5^\circ\text{C}$  using a disintegration apparatus (Electrolab, TDT-06T, Mumbai, India), according to EP (2002) specifications. The disintegration time was defined as the time necessary for the oral disintegrating tablet to completely disintegrate until no solid residue remains or only a trace amount of soft residue remains on the screen. A digital stopwatch was used to measure the disintegration time to the nearest second. Only one tablet was analysed at a time in order to ensure accuracy. All results are presented as

mean value of six readings with standard deviation (15,18).

#### **In vitro drug release study**

*In vitro* drug release was studied using LabIndia Dissolution Apparatus, with 900 ml of dissolution medium (phosphate buffer pH 6.6) maintained at  $37 \pm 1^\circ\text{C}$  for 90 min, at 100 rpm. 5ml of sample was withdrawn at particular time interval, and was replaced by an equal volume of fresh dissolution medium of same pH (phosphate buffer pH 6.6). Collected samples were analysed spectrophotometrically at measured wavelength of 220 nm and cumulative percent drug release was calculated. Formulated tablets disintegrate within 2 min, so dissolution studies were performed in the pH of mouth i.e. 6.5 to 6.8 (18,19).

The data obtained in the *in-vitro* dissolution study was analysed in terms of percentage drug release with respect to time (min).

#### **Stability study**

Selected tablets of all formulations were stored in polyvinyl chloride (PVC) blisters covered with aluminum foil at room temperature and 60% relative humidity, for a time period of 12 months. To maintain relative humidity, ammonium nitrate ( $\text{NH}_4\text{NO}_3$ ) saturated salt solution was used as a humidifier. Stability of all formulations was assessed by comparing the results from *in vitro* disintegration and dissolution studies. To investigate any change in the physico-chemical property of coacervates and drug, infrared spectrum were matched after 0, 3, 6 and 12 months. The results were checked for statistical significance using one-way analysis of variance (ANOVA). F-test was used for testing the equality of several means. A p-value  $> 0.05$  was considered statistically insignificant (20,21).

## **RESULTS**

Infrared spectra of different polymers were used to study the compatibility between them (Figure 1). It is well known that gum Arabic is an anionic polymer showing characteristic IR peaks in the range of

**Table 1.** Formula to prepare chitosan- gum Arabic coacervates based tablets

Ingredients	Formulations					
	BatchF1 (5%) <sup>a</sup>	BatchF2 (10%)	BatchF3 (20%)	BatchF4 (30%)	BatchF5 (40%)	BatchF6 (50%)
Drug (mg)	30	30	30	30	30	30
Coacervates (mg)	25	50	100	150	200	250
Sodium CMC (mg)	435	410	360	310	260	210
Magnesium stearate (mg)	10	10	10	10	10	10

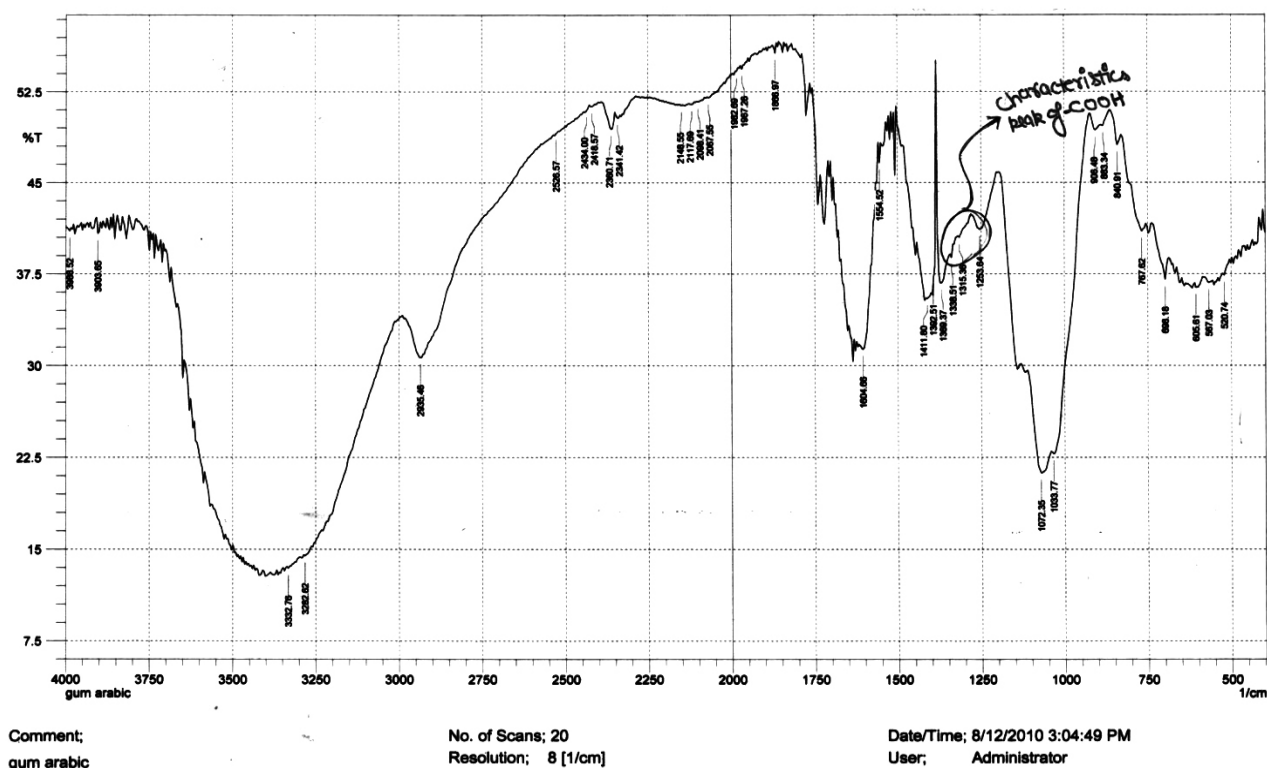
<sup>a</sup> percentage of total tablet weight

1500-1690 cm<sup>-1</sup>. This is a peak of primary amine group (-N-H). Same thing was found with chitosan, which was a cationic polymer with a characteristic peak in the range of 100-1320 cm<sup>-1</sup> (C-O bond). IR spectrum of chitosan-gum Arabic coacervates did not show these characteristic peaks, which easily strengthened the fact that an interaction was found between these polyelectrolyte groups (14). Characteristic peaks of drug were retained in the IR spectrum of mixture of drug and coacervates, which helped to easily predict

the fact that there was no interaction between drug and coacervates.

Chitosan- gum Arabic coacervates were evaluated for surface properties. Scanning electron microscopic study showed that chitosan- gum Arabic coacervates had very smooth and crystalline structure (Figure 2).

Particle size of prepared coacervates ranged from 157.9 to 200.3 μm. Furthermore, micromeritic study



**Figure 1A**

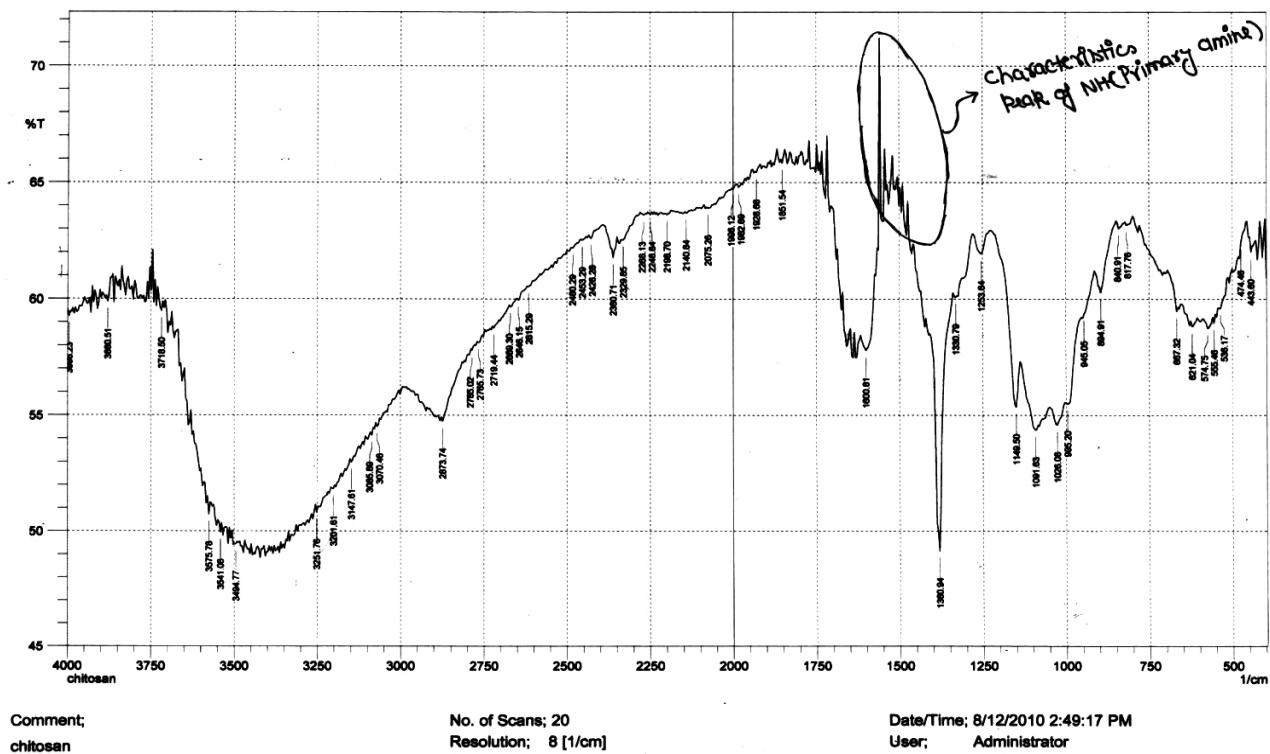


Figure 1B

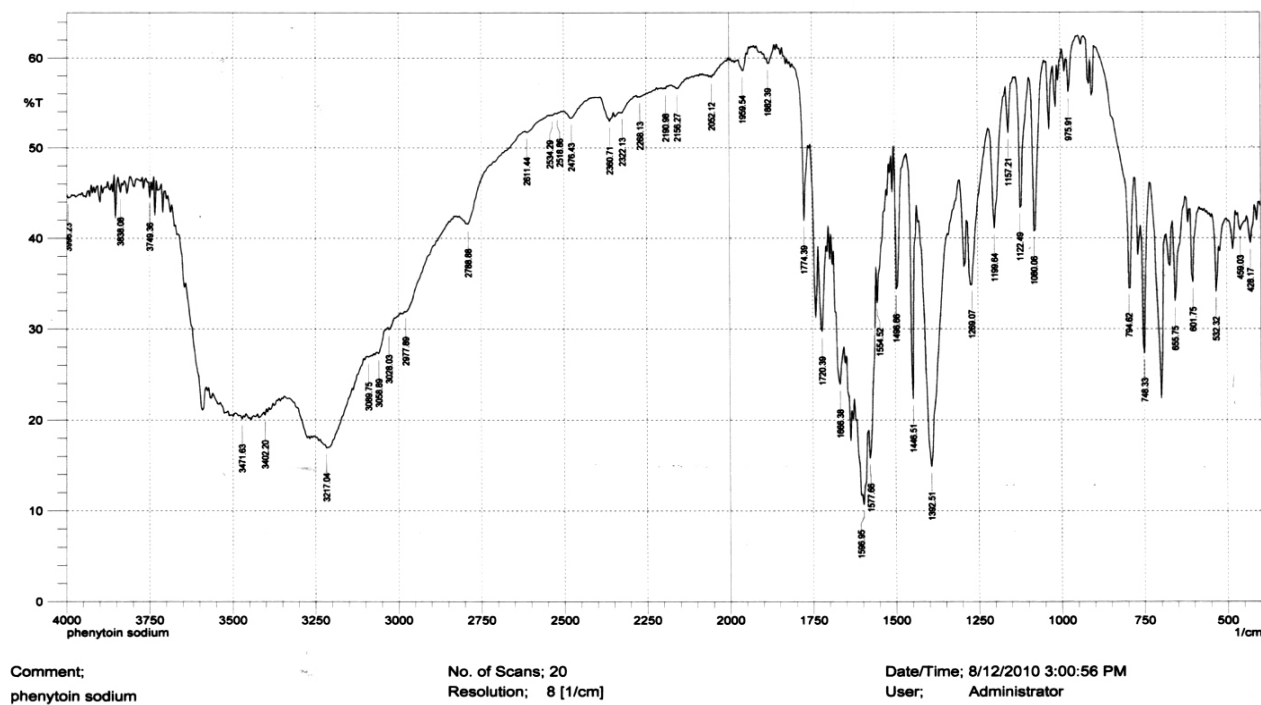


Figure 1C

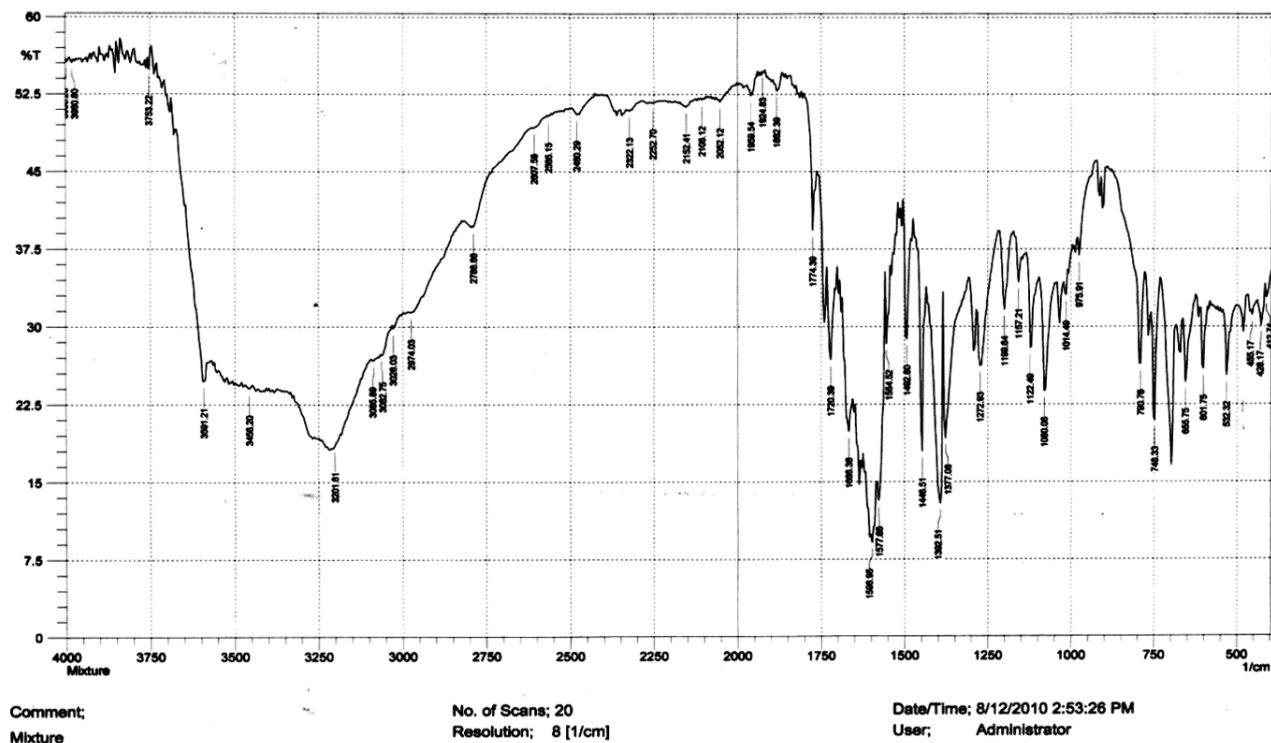


Figure 1D

Figure 1: Infra red spectrum of (a) gum Arabic (b) chitosan (c) phenytoin sodium (d) mixture of chitosan-gum arabic coacervates and drug.

and flow properties of coacervates were shown in table 2. As per the table 3, the formulated matrix tablets met the Pharmacopoeial requirement of uniformity of weight. They confirmed the requirement of the

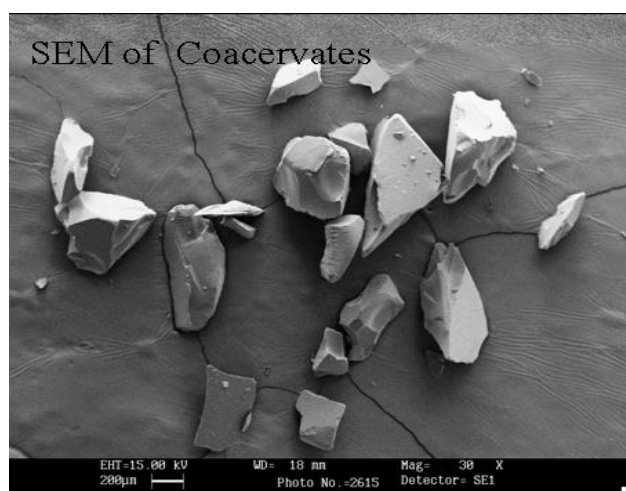


Figure 2. Scanning electron microscopy (SEM) study of coacervates.

assay as per USP. Hardness, percentage friability and thickness were all within acceptable limits. The hardness of tablets was found to be in the range of 20.03 to 20.1 N. This showed that tablets have uniform and sufficient hardness. It has been already found by Malviya et al that tablets prepared with natural polymers (pectin and gum Arabic) and semisynthetic polymer (sodium starch glycolate) have relatively lower hardness values (22, 23). Srivastava et al had already found the same range of hardness while evaluating binding properties of orange peel derived pectin (24). This strengthens the fact that tablets fabricated using chitosan-gum Arabic coacervates have ease of handling and require less attention for transportation. Friability was obtained between 0.098 to 0.33%, which was below 1% indicating sufficient mechanical integrity of the tablets. The two studies viz. hardness and friability indicate good mechanical strength of tablets. Thickness of tablets was also measured to evaluate efficacy of process of formulation development. Thickness of tablet was

found in between 3.77 to 4.02 mm. Drug content was also measured to evaluate the efficiency of process of formulation. Good and uniform drug content values for all batches are able to show that this particular process was highly efficient for fast disintegrating tablet formulations, required in the treatment of chronic disorders.

*In vitro* release study of formulated tablet was carried out as per specified conditions. Batch F2 showed best release characteristics in terms of disintegration time and percentage drug release. A graph between percentage drug release (Figure 3) and time was plotted, which showed that F2 gave maximum release within minimum time span.

After 12 months of stability study at controlled environmental conditions no significant differences ( $p < .05$ ) in disintegration time and drug release rate of the prepared tablets were observed. On the basis of infrared spectroscopic studies during the stability study, it was concluded that there was no change in the physico-chemical properties of both coacervates and drug.

## DISCUSSION

Findings of present investigation demonstrate that the properties of composite are entirely different from each of the individual polymer from which

this complex is formulated. It has been concluded from the IR spectrum study of compounds that polyelectrolyte like, chitosan and gum Arabic interact with each other due to their opposite charges and no interactions has been observed between drug and coacervates. Synthesized polymer has characteristic properties in terms of micromeritic studies and flow behaviour (Table 2). Micromeritic study data is important in predicting the flow property of polymer as well as granules obtained after granulation. The prepared complex has showed better flow properties, hence, depicting the fact that this chitosan- gum Arabic coacervates when used as polymer would enhance the flow characteristic of the formed granules. Flow property is taken into major consideration because it helps decide the ease of compaction of powder or granules into a tablet dosage form. Carr's index has been studied with the aim to evaluate compressibility characteristics of the composite complex. All these parameters have ranged within the official limits. The results have also revealed the fact (Table 3) that micromeritic properties and flow characteristics do not change significantly when different powder blends are prepared using composite. Post-compression studies including hardness and friability have all been in acceptable limits. These are the important physical properties which demonstrate that the tablet formulated can be

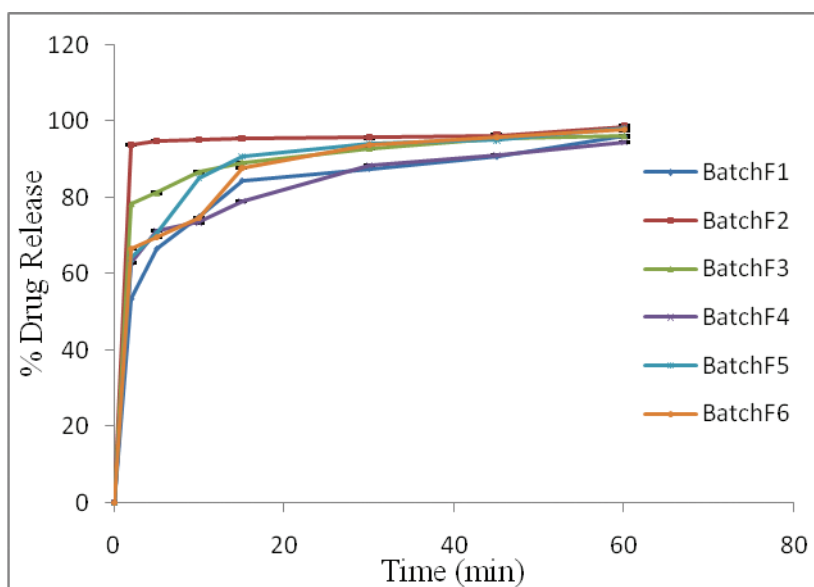


Figure 3. Release study of chitosan- guar gum coacervates tablets



**Table 2.** Characterization of coacervates<sup>§</sup>

Bulk density (mg/ml)	Tapped density (mg/ml)	Carr's index	Hausner's ratio	Bulkiness (ml/mg)	Angle of repose (θ)
0.589 ±0.0161	0.683 ±0.0382	13.8 ±0.0213	1.16 ±0.0162	1.70 ±0.0434	18.0 ±0.0197

<sup>§</sup> value with ± show standard deviation.

**Table 3.** Tablet evaluation parameters\*

Parameters	Formulations					
	F1	F2	F3	F4	F5	F6
Weight variation (mg)	501 ±0.0153	500.3 ±0.0212	500.1 ±0.0321	500.03 ±0.00901	500.08 ±0.0328	501 ±0.0177
Friability (%)	0.098 ±0.00961	0.232 ±0.0173	0.173 ±0.0531	0.204 ±0.0293	0.0691 ±0.0516	0.327 ±0.0432
Thickness (mm)	3.77 ±0.00801	3.78 ±0.00504	3.82 ±0.00511	3.91 ±0.0101	3.97 ±0.0102	4.02 ±0.00501
Hardness (N)	20.05 ±0.0581	20.08 ±0.0502	20.1 ±0.0821	20.08 ±0.0963	20.08 ±0.0962	20.03 ±0.0597
<i>In vitro</i> disintegration (sec)	0:15:5 ±0.00311	0:15:4 ±0.00702	0:20:01 ±0.0113	0:60:6 ±0.00708	0:30:5 ±0.0191	0:30:5 ±0.0122
Drug content (mg)	29.9 ±0.0312	29.9 ±0.0471	29.9 ±0.0511	29.9 ±0.0231	29.9 ±0.0195	29.9 ±0.0353
Drug release (%)	96.02 ±0.0532	98.6 ±0.0443	96.1 ±0.0353	94.4 ±0.0273	98.1 ±0.191	97.8 ±0.0242

\* values with ± shows standard deviation (n=3).

handled easily without any physical damage. These two data show the importance of formulation over commercial fast disintegrating tablets which have demerits of loss during transportation and storage. Thickness of tablets was also measured to evaluate efficacy of process of formulation development. Almost uniform thickness showed that applied procedure is efficient to produce such types of tablet. Drug content has also been accounted with an aim to evaluate the efficacy of process of formulation. Uniform drug content values for all batches show that this particular process is highly efficient and can be commercialized to formulate fast disintegrating tablet. The drug release is studied in terms of % drug release Vs time (min) graph, which shows that all batches have released drug within a small duration of time.

Data obtained during stability study demonstrate the fact that these tablets are stable during the period

of stability study (Table 4). Properties of tablets have not been changed significantly during the study. So these types of tablets can be stored in the environmental condition (temperature 25°C, relative humidity 40 to 60%).

It can be concluded by all the physico-chemical parameters and *in vitro* disintegration and *in vivo* dissolution study that batch F2 can be characterized as optimized formulation among the six batches of tablets prepared using composite as polymer. This batch has showed less friability and greater hardness when compared to other batches. *In vitro* disintegration time and *in vivo* dissolution time have been less comparative. These tablets released 98.63% of drug, which is quite better than other batches. On behalf of obtained results it was found that neither the drug nor the polymers showed any interaction, thus, removing the uncertainty of the cause of any chemical interaction. This is of utmost importance

**Table 4.** Stability studies of coacervates based tablets after 0, 6 and 12month storage at room temperature and 60% relative humidity<sup>1</sup>.

Attributes	0 months	3 months	6 months	12 months
<b>BatchF1</b>				
Disintegration time (sec)	0:15:5 ±0.00637	0:15:5 ±0.0571	0:15:5 ±0.0128	0:15:5 ±0.0341
Drug released after 2 min (%)	53.4 ±0.0331	54.1 ±0.0237	54.7 ±0.0234	54.2 ±0.0192
<b>BatchF3</b>				
Disintegration time (sec)	0:20:00 ±0.0342	0:20:05 ±0.0136	0:20:1 ±0.0191	0:20:1 ±0.0272
Drug released after 2 min (%)	78.3 ±0.0242	79.02 ±0.0262	77.4 ±0.0237	77.7 ±0.0165
<b>BatchF5</b>				
Disintegration time (sec)	0:30:5 ±0.0191	0:30:5 ±0.0246	0:30:6 ±0.0133	0:30:6 ±0.0191
Drug released after 2 min (%)	64.03 ±0.0192	64.9 ±0.0217	64.6 ±0.0176	64.4 ±0.0302

<sup>1</sup> values with ±shows standard deviation

while formulating any dosage form, as it enables the individual characteristics of compound to be retained.

## CONCLUSIONS

The study demonstrated that no physical interaction took place during the process of formation of chitosan-gum Arabic composite. It can be concluded that the presence and interaction of two different polymer solutions may lead to formation of a characteristic composite which can prove to enhance the release of drug from the tablet dosage forms within few minutes. Moreover, both the interacting species are of natural origin; thus, the polymer so formed shall prove to be a preferred one while designing fast disintegrating dosage form. The above research may, thus, prove to have high relevance on commercial scale keeping the fact that this complex exhibits such type of behaviour only in limited concentration range. These may overall prove to be efficient means of formulating fast disintegrating tablets and chitosan-gum Arabic coacervates stand as a potential candidate to be incorporated in dosage form meant

for the treatment of chronic disorders at the initial stage of chronic attack.

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