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# PREFORMULATION AND REHOLOGICAL CHARACTERIZATION OF VARIOUS POLYMERS FOR MUCOADHESIVE DRUG DELIVERY

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***ABSTRACT***
*Most of the pharmaceutical processes involved in the manufacturing of solid dosage forms are connected with powder flow properties. In present investigation powder flow characteristics of polymers such as sodium alginate, chitosan and Guar gum were carried out. Various measurements such as Tap density, bulk density, Angle of repose, hausner's ratio and percent compressibility were carried out to determine the flowability of polymers. Polymers were determined to investigate the effect of polymer sticking to mucosal linings. Swelling behavior of polymers was studied to check the control release properties of polymers. Sodium alginate is best polymer for mucoadhesive drug delivery amongst all used polymers as it gives highest mucoadhesive strength, viscosity and Shear stress of 14.10 gm, 4800 m pas and 118.24 gm respectively. From the obtained result it can be concluded that the polymers were having good flow properties, mucoadhesive strength and predictable swelling. Therefore these polymers can be better alternatives if used in proper combinations to have effective mucoadhesive drug delivery system.*

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**Key words:** Flow properties, Mucoadhesion, Sodium alginate, Chitosan, Guar gum.

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## INTRODUCTION

The preparation of essentially all dosage forms involves the handling of solid materials. Among all finished products, solid dosage forms are the most predominant in terms of volume and value. The importance of solid-handling properties, especially flow properties, cannot not be overemphasized. The flow properties of solids have great impact on the tableting and encapsulation processes since these dosage form manufacturing processes require the flow of powder materials from a storage container to filling stations, such as tablet dies or capsule fillers (1). Different flow properties are required at different stages of processing and should be carefully taken into consideration during formulation and process validation. Kinetics of mixing is influenced by the physical state of the active constituent (2). During a pharmaceutical process, most of the steps such as sieving, pouring, micronizing, mixing, pneumatic conveying, grinding, drying, compaction, are connected with the powders flowability (3). Flow properties of powder must be studied in terms of quality control of raw materials in order to maintain product uniformity but also to avoid rigid situations in which process breakdown may occur, with respect to imposed conditions. Consequently, powder flow properties should be measured and optimized as part of every development program (4). Powder flow characteristics are commonly investigated under gravity loading conditions using measurements such as the angle of repose and other handling angles (5), standardized flow rate (6), apparent and 'tapped' densities and derived indices such as defined by Carr (1965a) or Hausner (1967).As the dimensions of particles increase, the forces acting on them change. Fine powder particles less than 100 *m*m in diameter are acted upon primarily by surface forces. Particles above 1000 *m*m in diameter are governed by gravitational forces. Therefore, the balance of interaction forces determines powder behavior (7).

**MATERIALS AND METHODS:**

**MATERIALS:**

Sodium alginate, Chitosan, and Guar gum were procured from (Loba Chemicals, Munbai ,India), All other chemicals purchased were of analytical grade.

**METHODS:**

**Characterization of powders (8):**

The powders were analyzed for physical appearance, powder nature, $P^H$ and solubility.

**Moisture Content:**

Moisture content of polymers was determined by Karl Fischer titrator (Matic D, Veego).

**Preparation of Tablets:**

Formulations were prepared using chitosan, sodium alginate and Guar gum and were mixed in various combinations (Table I, II). Powdered mass was then passed through 40-mesh screen. The tablets were compressed by direct compression method by using tablet Punching Machine – Karnavati - Minipress D-II Link.

**Table no. 1.** Formulation of tablet using sodium alginate and chitosan.

| **Ingredients** | Formulations | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 |
| **Sodium alginate (mg)** | 20 | 20 | 30 | 30 | 20 | 30 | 10 | 30 | 30 | 30 |
| **Chitosan (mg)** | 65 | 100 | 65 | 100 | 30 | 30 | 30 | 20 | 10 | 05 |
| **Tablet total weight (mg)** | 85 | 120 | 95 | 130 | 50 | 60 | 40 | 50 | 40 | 35 |

**Table no. 2.** Formulation of tablet using Guar gum and chitosan

| **Ingredients** | Formulations | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | G1 | G 2 | G 3 | G 4 | G 5 | G 6 | G 7 | G 8 |
| **Guar gum (mg)** | 60 | 60 | 50 | 50 | 40 | 40 | 30 | 25 |
| **Chitosan (mg)** | 10 | 05 | 10 | 05 | 10 | 05 | 10 | 05 |
| **Tablet total weight (mg)** | 70 | 65 | 60 | 55 | 50 | 45 | 40 | 30 |

**Polymer characterization (9):**

Individual Polymers and various formulations of polymers were evaluated for the following powder characteristics;

**Bulk density:**

A sample powder was introduced in 100 ml graduated cylinder. The volume of the material was noted on graduated cylinder. The bulk density was calculated by the formula given below;

$$P_0 = M/V_0$$

Where, $\rho_0$ = Bulk density
M = Mass of the sample powder,
$V_0$ = volume of the powder.

**Tap density:**

A sample powder was filled in 100 ml graduated cylinder. The mechanical tapping was carried out and the tapped volume $V_f$ was noted.

$$P_t = M/V_f$$

Where, $\rho_t$ = tapped density
M = weight of the sample powder,
$V_f$ = tapped volume of the powder.

**Compressibility index:**

The bulk density and tapped density was measured and compressibility index was calculated using the formula;

$$\%\ compressibility = P_t - P_0 / P_t \,.\, 100$$

Where, $\rho_t$ = tapped density
$\rho_0$ = bulk density

**Angle of repose:**

The angle of repose gives an indication of the flow ability of the substance. Funnel was adjusted such that the tip of the funnel lies 2 cm above the horizontal surface. The drug powder was allowed to flow from the funnel under the gravitational force till the tip of the pile just touched the tip of the funnel of orifice size 6 mm, so the height of the funnel was taken as 2 cm. The diameter of the pile was determined by drawing a boundary along the circumference of the pile and taking the average of six diameters. These values of height and diameter were then substituted in the following equation.

$$\theta = \tan^{-1} (2h / d)$$

Where, θ is angle of repose
h is height of the pile and
d is the diameter of the pile.
The experiment was done in triplicate.

**Hausner ratio**

Hausner ratio was calculated using the formula;

$$\text{Hausner ratio} = \rho_t / \rho_o$$

Where, $\rho_t$ = tapped density
$\rho_0$ = bulk density.

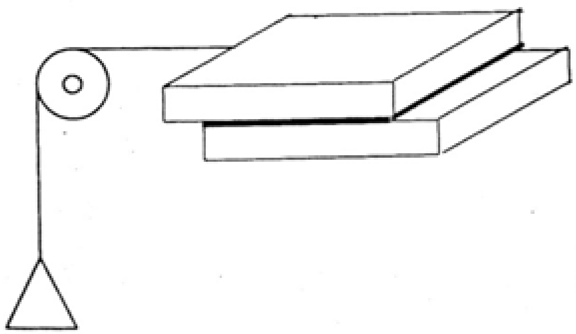
**Determination of viscosity (10, 11, 12)**

Polymeric solutions of 1% w/v were prepared in 100ml of water. The viscosities of prepared polymeric solution were determined using Brookfield viscometer cap2000+. Suitable spindle and rpm were selected and viscosity was determined.

**Shear stress measurement (13, 14)**

To smooth, polished plexi glass block were selected. One block was fixed with adhesive on a glass plate which was then fixed on the leveled table. The level was adjusted with the spirit lamp. To the upper plate with the help of the plastic block. The thread was tied and it was passed down through pulley. The length of the thread from the pulley to pan was approximately 17 cm, was attached in to which the weight can be added. The assembly was shown as follows (figure 3).

**Figure No.3.** Shear stress measurement apparatus



**Shear-stress measurement.**

**Procedure:** Different polymer solutions of 2 %w/v strength were prepared using water as a solvent. A fixed amount (one drop) of polymer solution was kept on the center of the adhered glass plate with the aid of pipette and the second block was placed on the first block and pressed by applying 100gm of weight such that the drop of polymer spreads as a uniform film between the two blocks. After keeping it for the fixed time intervals of 5 min, 10 min and 15 min, and the weights were added into the pan. The weight just sufficient to pull the upper block will represent the Adhesion strength. It is the Shear Stress value.

**Measurement of the mucoadhesive strength (15,16)**

For measurement of the mucoadhesive strength pure polymer was taken and the disc of 300mg. was prepared by using 11mm flat punch on the karnavati, Minipress D-II Link G and used for the measurement of the mucoadhesive strength.

**Instrument**

The apparatus was locally assembled and was a modification of the apparatus applied by Parodi et al. The device was mainly composed of a two-arm balance. The left arm of the balance was replaced by small copper lamina plate vertically suspended through a wire. At the same side, a movable platform was maintained in the bottom in order to fix the model mucosal membrane.

**Ex vivo mucoadhesion studies on polymers**

The above described instrument was used with sheep stomach mucosa as model membrane. The mucosal membrane was excised by removing the underlying connective and adipose tissue, and equilibrated at 37°C± 1°C for 30min in pH 1.2 simulated gastric juice before the bioadhesion evaluation study. The polymeric disc was lowered onto the mucosa under a constant weight of 5g for a total contact period of 1 min . Bioadhesive strength was assessed in terms of the weight in grams required to detach the tablet from the membrane.

**Swelling study (17)**

The swelling of the polymers can be measured by their ability to absorb water and swell. The swelling property of the formulation was determined by various techniques. The water uptake study of the tablet was done using USP dissolution apparatus II. The medium used was 900 ml of 0.1N HCL, rotated speed of paddle was kept 100 rpm. The medium was maintained at 37±0.5 $^{o}$C through out the study. After a selected time intervals, the tablets were withdrawn, blotted to remove excess water and weighed. The weight of the swollen tablet was calculated. The swelling index (S.I.) was determined from the following relation:

$$\text{Swelling Index (\%)} = (W_t - W_0 / W_0).100$$

Where, $W_t$ is the weight of the swollen tablet at each interval t,

$W_o$ is initial wt of the tablet.

**RESULT AND DISCUSSION**

**Characterization of powder:**

Powders were evaluated for physical appearance, powder nature; $P^H$ and solubility, the result of present data suggest that the evaluated parameters are in the prescribed range of official standards.

**Moisture Content**

Moisture content of various polymers was depicted in table no. 4. Results shows that moisture content of all the polymers were within the prescribed limit that they should contain less than 5% of moisture.

**Polymer Characterization**

Bulk density, Tap density, Compressibility Index, Angle of repose and Hausner ratio of Sodium alginate, Guar gum, Chitosan and various prepared formulations were depicted in Table no.3, 6 and 7 respectively. The result shows that polymers have % Compressibility within the prescribed limits i.e.

all the individual polymers is having % Compressibility between 11-15 ( Table no.3 ) which suggest that polymers are having good flow properties and can be used for direct compression. Results of angle of repose suggest that all Values are within the range of 25-30 degree (Table no.3) denoting excellent flow properties of polymers.If the values for Hausner ratio is nearer to 1 it signifies that the material is having excellent flow properties, data obtained from the study gives a clear idea about the same i.e. material is having Hausner ratio value nearer to 1 (Table no.3) and therefore it describes the excellent flow properties of polymers.

**Table no. 3.** Powder characterization of Polymer.

| Polymers | Parameter | | | | |
|---|---|---|---|---|---|
| | Bulk density (g/ml) | Tap density (g/ml) | Compress-ibility (%) | Angle of Repose($^0$) | Hausner ratio |
| Sodium alginate | 0.62±0.01 | 0.72 ±0.01 | 13.85 | 25.69 ±0.14 | 1.161 |
| Guar gum | 0.66±0.03 | 0.74 ±0.01 | 14.60 | 25.79 ±0.57 | 1.121 |
| Chitosan | 0.61±0.04 | 0.74 ±0.01 | 14.78 | 25.19 ±0.35 | 1.213 |


| Polymers | Parameter | | | | |
|---|---|---|---|---|---|
| | Bulk density (g/ml) | Tap density (g/ml) | Compress-ibility (%) | Angle of Repose($^0$) | Hausner ratio |
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| Chitosan | 0.61±0.04 | 0.74 ±0.01 | 14.78 | 25.19 ±0.35 | 1.213 |


* Mean ± S.D. for n=3

**Table No. 6.** Polymer characterization of formulations containing sodium alginate and chitosan.

| Parameters | Formulations | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 |
| **Bulk density (g/ml)** | 0.66 | 061 | 0.63 | 0.62 | 0.62 | 0.66 | 0.61 | 0.63 | 0.58 | 0.59 |
| **Tap density (g/ml)** | 0.74 | 0.74 | 0.77 | 0.72 | 0.72 | 0.74 | 0.74 | 0.77 | 0.78 | 0.72 |
| **Compressibility (%)** | 17.60 | 17.56 | 18.18 | 16.85 | 16.85 | 17.60 | 17.56 | 18.18 | 19.12 | 16.75 |
| **Angle of repose ($^0$)** | 27.23 | 27.23 | 17.02 | 24.69 | 24.69 | 24.79 | 24.19 | 25.69 | 25.79 | 24.69 |

**Table No. 7.** Polymer characterization of formulations containing guar gum and chitosan.

| **Parameters** | Formulations | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | G1 | G 2 | G 3 | G 4 | G 5 | G 6 | G 7 | G 8 |
| **Bulk density (g/ml)** | 0.58 | 0.63 | 0.58 | 0.66 | 0.76 | 0.63 | 0.61 | 0.59 |
| **Tap density (g/ml)** | 0.74 | 0.77 | 0.78 | 0.74 | 0.90 | 0.77 | 0.74 | 0.72 |
| **Compressibility (%)** | 17.60 | 18.18 | 19.12 | 17.62 | 15.37 | 18.18 | 17.56 | 16.75 |
| **Angle of repose ($^0$)** | 25.69 | 24.21 | 26.12 | 22.62 | 32.69 | 24.69 | 24.21 | 25.69 |

**Determination of viscosity:**

The polymers were also evaluated with respect to some specific parameters that included the measurement of viscosity. From table no.4 it can be seen that sodium alginate has higher viscosity of 4800 mpas as compaire to chitosan and guar gum (4750 mpas and 4610 mpas respectively). Higher the viscosity of the polymer greater was the swelling capacity which leads to stronger adhesion of polymer to mucosa (18).

**Table No. 4.** Parametric evaluation of polymers.

| **Polymer** | **Moisture content (%)** | **Mucoadhesive Strength (gm) ±SEM** | **Viscosity (m Pas) ±SEM** |
|---|---|---|---|
| **Sodium alginate** | 4.2 | 14.10 ± 0.132 | 4800 ±0.025 |
| **Guar gum** | 3.4 | 12.9 ± 0.010 | 4610 ± 0.019 |
| **Chitosan** | 4.1 | 10.1 ± 0.020 | 4750 ± 0.024 |

* Mean ± S.D for n=3

**Shear stress measurement**

The results of shear stress measurement, the weight required to break the adhesion recorded for various polymers with different contact times are shown in table no.5. From the obtained results it can be seen that increasing contact time for adhesion increases the force required in terms of weight for all the polymers ultimately results in increasing the adhesion strength.

**Table No. 5.** Shear stress measurement of various polymers.

| **Polymers studied** | **Shear stress measurement (gms)** | | |
|---|---|---|---|
| | **After 5 mins** | **After 10 mins** | **After 15 mins** |
| **Sodium alginate** | 75.04 ± 0.76 | 87.21 ± 3.98 | 118.24 ±2.58 |
| **Guar gum** | 64.08 ± 2.85 | 70.11 ± 3.35 | 90.01 ± 2.57 |
| **Chitosan** | 68.30 ± 1.15 | 75.22 ± 1.02 | 102.12 ± 2.50 |

* Mean ± S.D. for n=3

It has been reported that adhesion is affected by hydration. Increasing the contact time might be reducing the hydration resulting due to evaporation facilitating higher adhesion (19). From the results, it can be seen that polymers having higher molecular weight, more number of polar groups and high viscosity exhibited higher adhesion.

**Measurement of the mucoadhesive strength**

Polymers show good individual mucoadhesion to stomach mucosa of sheep. Sodium alginate show greater mucoadhesion of 14.10 gm than that of guar gum and chitosan which shows mucoadhesion strength of 12.9 and 10.1 gms respectively.

***Swelling Study***

Swelling index values of tablets comprising of Sodium alginate, Guar gum and Chitosan are shown in figure no.1 and 2. As the amount of the polymer in the formulations increases, the swelling increases for all the polymers. Results of the study represent the use of these polymers in controlled drug delivery systems.In Formulation F1 to F10, high initial swelling was observed with erosion in the latter stages. This high initial swelling was observed due to more amount of Chitosan present in the formulation. Guar gum does not swell rapidly. It swells slowly initially and hence initial burst release of drug from the guar gum matrices can be observed. Figure no. 1 shows formulation F2 swells more i.e. 302.3% in 8 hrs. This is because it contains more amount of Chitosan. Above results suggest that tablet having higher amount of Chitosan swell rapidly and to higher extent while the tablet containing guar gum swell to lesser extent.

**Figure no.1.** Swelling study for tablets containing Sodium alginate and Chitosan

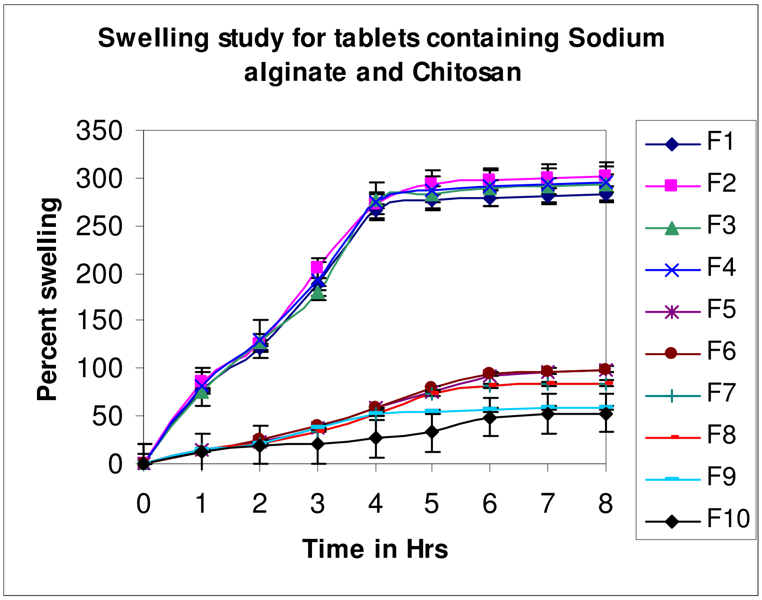
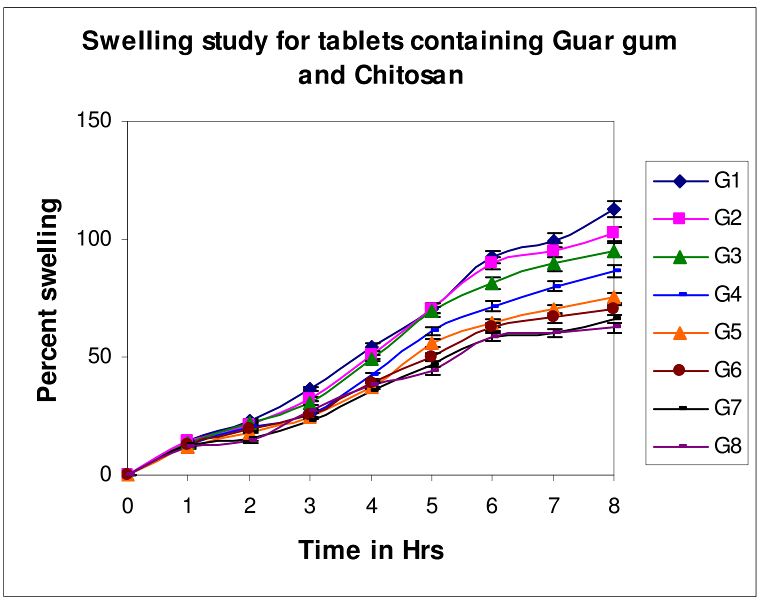



**Figure no. 2. Swelling study for tablets containing Guar gum and Chitosan**




**CONCLUSION**

Flow properties are one of the most important aspects for the designing, formulating and maintaining quality of any pharmaceutical product. Present study demonstrates the importance of rehological properties of various polymers such as sodium alginate, Guar gum and Chitosan. All polymers used shows good flow behavior. Result of shear stress, mucoadhesion and viscosities showed importance of sodium alginate in mucoadhesive drug delivery as it gives better results among all polymers used. Swelling indices of polymers give an idea about use of these polymers in controlled mucoadhesive drug delivery. Finally it can be concluded that sodium alginate, Guar gum and Chitosan if used in proper combinations can be a better alternatives to have effective mucoadhesive drug delivery system.

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