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INFLUENCE OF CHITOSAN CONCENTRATION ON MECHANICAL AND RELEASE PROPERTIES OF METRONIDAZOLE TABLET

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Abstract

Background: Chitosan is a widely used pharmaceutical polymer and it serves different purposes in tablet formulations.
Objective of study: This work was aimed at assessing the impact of chitosan concentration on the mechanical and release properties of metronidazole tablet.
Methodology: Seven batches of metronidazole tablets (500 mg weight) containing 40 % drug and 33 % microcrystalline cellulose were made to contain crab shell chitosan at concentrations of 0, 2.5, 5.0, 7.5, 10, 15 and 20 %w/w for batches 1–7 respectively and then produced by direct compression. The tablets were assessed for crushing strength, friability, compact density, disintegration time and dissolution rate. Porosity, crushing strength–friability index (CS-FR) and crushing strength-friability-disintegration time index [(CS-FR)/DT] were calculated. Data were analyzed using GraphPad Instat-3 software.
Results: Crushing strength decreased while friability and porosity increased with increase in concentration of chitosan. The disintegration times were 4.54, 2.49, 12.66, 16.85, 18.29, 22.26 and 32.97 min for F1, F2, F3, F4, F5, F6 and F7 respectively. There were significant differences in both CS-FR and (CS-FR)/DT indices. The (CS-FR)/DT indices were 5.04, 6.18, 1.00, 0.71, 0.56, 0.40 and 0.22 for F1 to F7 respectively. Dissolution rate decreased with increase in chitosan concentration.
Conclusion: Low concentrations of chitosan (5.0 %w/w and below) in tablets are characterized by good mechanical and immediate release properties. The use of chitosan at higher concentration for any purpose should be in conjunction with an excipient that will impart good mechanical strength.
Keywords: Crab shell chitosan, mechanical properties, release properties.
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Introduction

Chitosan is a unique excipient that can be utilized to serve several functions in pharmaceutical formulations [1]. It can be used as a binder in wet granulation, as a diluent in direct compression, as a tablet disintegrant and as a permeation enhancer [2]. Hence, it influences the manufacture and performance of tablet formulations.

Since crushing strength reflects tablet's strength and friability reflects its weakness, the crushing strength – friability index (CS-FR) is an expression of the mechanical properties of tablet [3]. An improvement of this index is the crushing strength – friability – disintegration time index [(CS-FR)/DT] which is an expression of the overall quality of tablet [3]. The (CS-FR)/DT reflects both mechanical and release properties of tablet. Tablet disintegration which is the initial step of drug release usually precedes drug dissolution [4].

A polymer can be utilized as a tableting excipient after considering its properties such as compatibility, flowability, disintegration qualities, hygroscopicity, lubricity and stability [5]. Chitosan does not cause any biological hazard and it possesses most of these desirable properties [6]. Previous work of Olorunsola *et al* [7] had shown the compatibility of chitosan with metronidazole and its suitability for direct compression. In that work, the concentrations of both microcrystalline cellulose and chitosan in the tablets were varied. Binary blends of microcrystalline cellulose and chitosan (in ratios 9:1, 4:1, 2:1 and 1:1) as direct compression excipients were compared with similar blends of microcrystalline cellulose and α-lactose monohydrate. It was observed that the tablets formed using the different binary blends of microcrystalline cellulose and chitosan manifested different behaviours in contrast to those of microcrystalline cellulose and α-lactose monohydrate which have similar release profile.

In the present report, the concentration of microcrystalline cellulose was constant while that of chitosan is varied. The aim is to determine the effect of chitosan concentration on the mechanical and release properties of directly compressed metronidazole tablet.

Materials and Methods

Materials

The materials used include: metronidazole powder (Hopkins and Williams, England), Art 2330 microcrystalline cellulose (E. Merck, Darmstadt) and chitosan derived from shells of *Callinectes gladiator* having degree of deacetylation of 62.7% [7]. Others are α-lactose monohydrate (Riedel De Haen Seelze, Hannover), magnesium stearate (BDH Poole, England), and talc (BDH Poole, England).

Composition of the tablet formulations

Seven (7) batches of tablet formulation were prepared based on Table 1. Batch 1 contained no chitosan while batches 2-7 contained chitosan in varying amounts as 2.5, 5.0, 7.5, 10, 15, and 20% respectively. Microcrystalline cellulose (33%) and metronidazole (40%) were present in all the batches. Lactose was used as the bulking agent. Magnesium stearate and talc were included in all the batches in quantities of 0.5% and 1.5% respectively. Calculation and preparation were made for 100 tablets per batch, tablet weight being 500 mg.

Table 1: Tablet formula

Ingredient	F1	F2	F3	F4	F5	F6	F7
Metronidazole (%)	40	40	40	40	40	40	40
Microcrystalline cellulose (%)	33	33	33	33	33	33	33
Chitosan (%)	0.0	2.5	5.0	7.5	10	15	20
Lactose (%)	25	22.5	20	17.5	15	10	5
Mg stearate (%)	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5

Preparation of the mix for direct compression

The active ingredient (metronidazole) and excipients (microcrystalline cellulose, lactose and chitosan) were weighed individually and triturated for 5 min. The true density (D_t) of each mix was determined by the specific gravity bottle method. A clean, dry 25 ml specific gravity bottle was filled with xylene and its weight was determined. Some of the xylene was poured out and 1 g sample was placed inside. More xylene was added until the bottle was filled and was wiped dry of excess fluid. Its weight was again determined. The true density (D_t) was calculated using the following equation:

$$Dt = \frac{w}{a+w-b} \; X \; SG \quad \ldots\ldots\ldots\ldots (1)$$

Where *w* is the weight of powder mix, *a* is the weight of bottle + xylene; *b* is the weight of bottle + xylene + powder mix and *SG* is the specific gravity of xylene.

Preparation of tablets

The required quantities of magnesium stearate and talc were weighed and added to the powder mix in the mortar and mixed together to obtain a homogeneous mixture. The mixture was then tableted using the F3 single punch tableting machine (Cadmach Machinery Co. PVT., India).

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Quality assessment of tablets

Porosity

Compact density (CD) of tablet was determined using the weight, diameter and thickness of three (3) tablets from each batch and by applying the following equation:

$$CD = m/\pi r^2 h \quad \ldots\ldots\ldots\ldots\ldots\ldots (2)$$

Where m = mass of tablet, r = radius and h = thickness.

Thereafter, the tablet porosity Φ was calculated using the following equation:

$$\Phi = 1 - \frac{CD}{D_t} \quad \ldots\ldots\ldots\ldots\ldots\ldots (3)$$

Where CD = compact (tablet) density and D_t = true density of the powder blend.

Crushing strength

A tablet was held diametrically in the jaws of a hardness tester (model MHT-20, Monsanto India) and the force in kg required to crush each tablet was noted. The mean of three determinations was taken for each batch.

Tensile strength

The tensile strength was calculated using the values of crushing strength, diameter and thickness of the same three (3) tablets from each batch.

$$T = 2F/\pi dt \quad \ldots\ldots\ldots\ldots\ldots\ldots (4)$$

Where F = crushing strength of tablet, d = diameter and t = thickness.

Friability
Ten (10) tablets were de-dusted, weighed together and placed in a drum of Roche friabilator (DT-2D, Roche, India). The tablets were tumbled for 4 min at a speed of 25 rev/min and afterward de-dusted and weighed again. The friability of tablet was calculated as the ratio of weight loss to initial weight of tablet expressed as percentage.

Crushing strength – friability index
The crushing strength - friability index (CS-FR) was calculated as the ratio of crushing strength to friability.

Disintegration time
Tablet disintegration was carried out using the disintegration tester consisting of a basket rack holding 6 plastic tubes. The basket was immersed in a bath of distilled water maintained at 37^{o}C. One (1) tablet was placed in each tube and a total of six (6) tablets were used per batch. A standard motor driven device was used to move the basket assembly at a frequency of 30 cycles/min. The tablets were allowed to disintegrate and the particles allowed to pass through the mesh screen. The time taken for complete disintegration of each tablet was noted.

Crushing strength – friability – disintegration time index
The Crushing strength - friability - disintegration time index [(CS-FR)/DT] of tablet was calculated as ratio of crushing strength - friability index to disintegration time

Dissolution rate
In-vitro dissolution test was carried out using the USP dissolution apparatus. One tablet was placed in each of the wire mesh basket suspended in a dissolution medium of 900 ml of 0.1 N HCl constantly maintained at 37 ± 1 ^{o}C. The baskets were rotated at a speed of 50 rpm and the experiment was allowed for 1 h. A 10 ml aliquot was withdrawn at 10 min intervals. Each sample was filtered through Whatman filter paper No.1 and the absorbance was taken at 278 nm using UV spectrophotometer (Jenway, England). A graph of cumulative percent drug released was plotted against time.

Statistical analysis
Data were expressed as mean ± standard error of mean. Statistical analysis was done using analysis of variance followed by Turkey-Kramer multiple comparison test using GraphPad Instat-3 software. Significance of difference was set at *p - value* less than 0.05.

Results and Discussion

A plot of porosity of tablet versus concentration of chitosan is shown in Figure 1. The porosity of the tablets generally increased with increase in concentration of chitosan. This can be explained by the poor compressibility of chitosan [7].

Porosity provides a good prediction of mechanical strength of tablet. High porosity suggests low mechanical strength [8]. Porosity also provides an estimation and explanation of how liquids enter into the tablet matrix [9]. It is an important critical quality attribute for both disintegration and bioavailability properties. Hence, the parameter is vital to the prediction of excipients' behaviours in tablet formulations.

A plot of tensile strength versus concentration of chitosan is shown in Figure

2. The tensile strength decreased as the concentration of chitosan was increased.

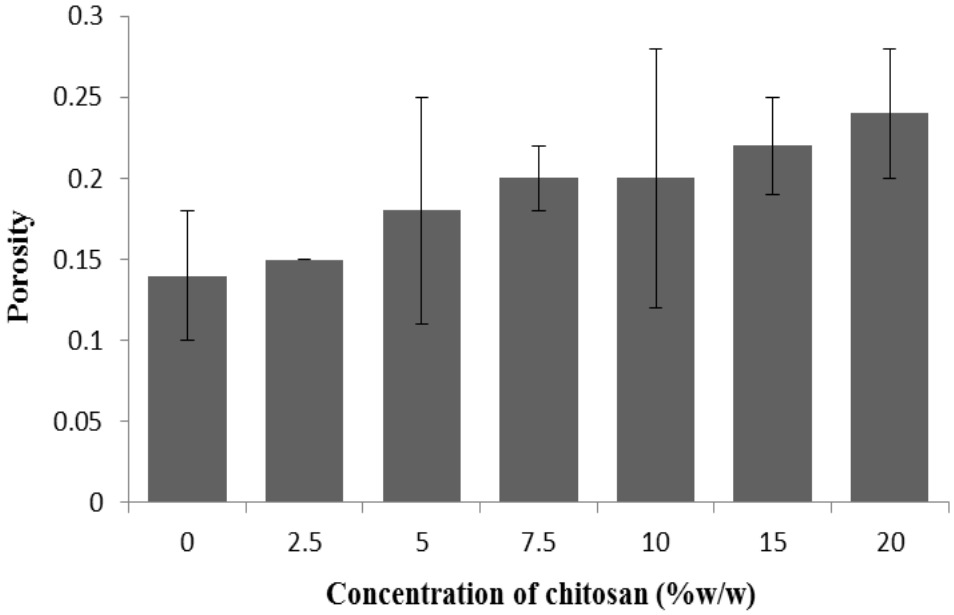

Figure 1: Plot of porosity versus concentration of chitosan

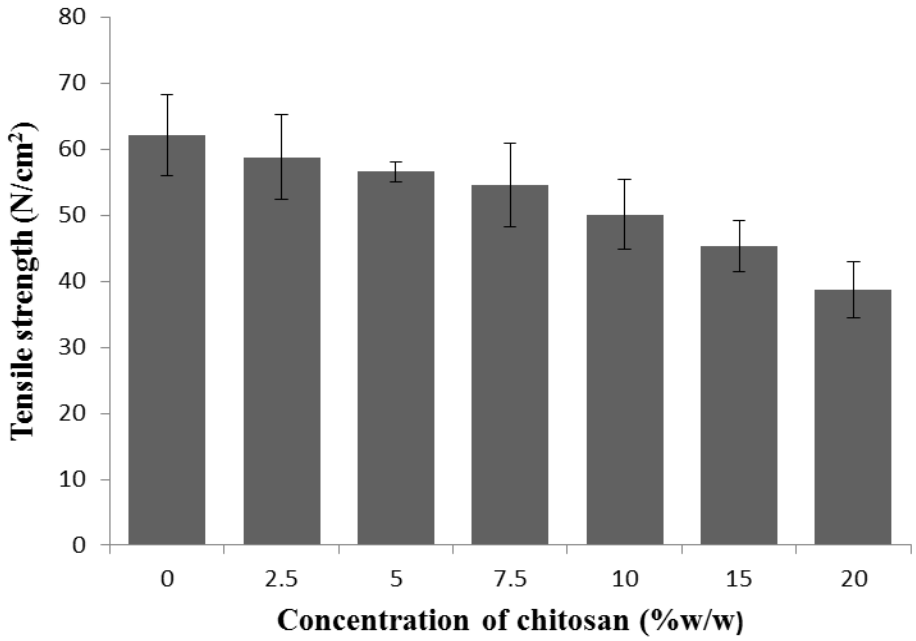

Figure 2: Plot of tensile strength versus concentration of chitosan

Tensile strength is a better measure of tablet strength compared to crushing strength because it takes into consideration the tablet dimensions [10]. The result showed an inverse relationship between chitosan concentration and tensile strength. Hence, caution must be taken in utilizing high concentration of chitosan in tablet formulation so as to avoid weak tablets. An appropriate precaution is to combine chitosan with an excipient that will impart strength.

The effect of chitosan concentration on some mechanical and release properties are shown in Table 2.

Table 2: Effect of chitosan concentration on quality indices of metronidazole tablet

Concentration of chitosan (%w/w)	CS-FR Index	Disintegration time (min)	(CS-FR)/DT Index
0.00	22.88 ± 3.17	4.54 ± 0.12	5.04 ± 0.29
2.50	15.39 ± 0.20	2.49 ± 0.36	6.18 ± 0.04
5.00	12.64 ± 0.89	12.66 ± 1.23	1.00 ± 0.75
7.50	11.92 ± 0.57	16.85 ± 0.68	0.71 ± 0.40
10.00	10.22 ± 0.58	18.29 ± 0.52	0.56 ± 0.21
15.00	8.98 ± 2.37	22.20 ± 0.48	0.40 ± 0.16
20.00	7.26 ± 0.95	32.92 ± 1.58	0.22 ± 0.01

The calculated crushing strength – friability index decreased with increase in chitosan concentration sequel to the decrease in the crushing strength and increase in the friability as the chitosan concentration was increased. The CS-FR decreased from 22.88 to 7.26 as the chitosan concentration was increased from 0 to 20%. The CS is a measure of tablet strength while FR is a measure of the weakness. Therefore, the higher the CS-FR, the stronger is the tablet [11].

Tablets containing 2.5% chitosan had the lowest disintegration time. This explains why chitosan is useful as super-disintegrant at low concentration [12]. Disintegration is a basic step prior to release (dissolution) of the active ingredient for absorption to take place. Only the tablets containing 0-5% chitosan passed the test for disintegration time (maximum of 15 min for immediate release tablets). Hence, concentrations of 7.5% chitosan and above are not suitable for formulation of immediate release tablet.

Even though tablets containing higher concentrations of chitosan are characterized by higher porosity, the disintegration times were longer. It can be inferred that at high concentration of chitosan, water penetration does not lead to disintegration but gelling.

Tablets containing 2.5% chitosan had the highest (CS-FR)/DT value. The parameter generally decreased with increase in chitosan concentration. The highest value of the parameter for tablets containing 2.5% chitosan is due to the associated lowest disintegration time. The (CS-FR)/DT ratio of a tablet formulation is an index of tablet quality which reflects tablet strength (crushing strength) as well as tablet weakness (friability) and at the same time evaluates any negative effects of these parameters on disintegration time [7, 13]. A

high value of the (CS-FR)/DT ratio indicates a good balance between binding and disintegration properties.

The dissolution profile of the tablet formulations are illustrated in Figure 3. The dissolution rate generally decreased with increase in chitosan concentration. This trend corresponds with the trend of the disintegration time. The dissolution rate of tablet containing 2.5% chitosan is comparable with that without chitosan

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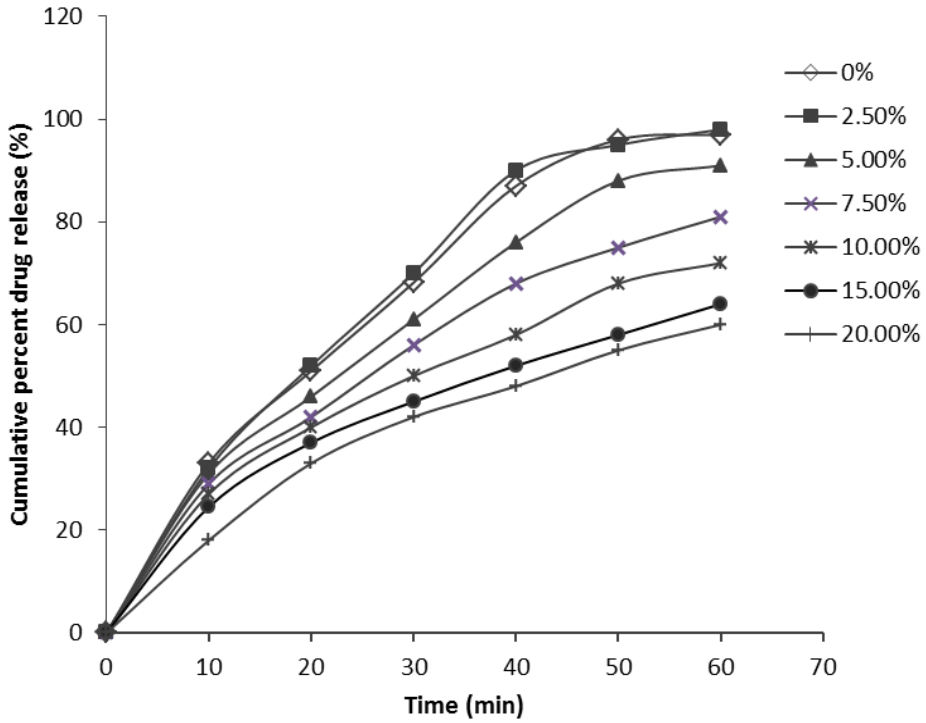

Figure 3: Plot of cumulative percent drug released versus time

According to United States Pharmacopoeia [14], there should be a minimum of 75% drug release within 1 h for immediate release tablets. Tablets containing 7.5% chitosan and below passed the dissolution test for immediate release tablet while the others failed. This result is slightly different from the disintegration test result where all tablets containing more than 5% chitosan failed the test. Higher concentrations of the polymer (> 7.5%) could be useful for sustained release formulation.

Conclusion

Inclusion of chitosan is associated with production of tablets having high porosity and low mechanical strength. The effect of the polymer on drug release depends on the concentration used. While low concentration is characterized by fast drug release, high concentration is characterized by slow release. Concentration of 2.5% is the optimum for production of immediate release tablets. Low concentrations of chitosan (5.0% and below) are characterized by good mechanical and release properties. The use of the polymer at higher

concentration for any purpose should be in conjunction with an excipient that will impart good mechanical strength.

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