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Original Research Article

Formulation and *In vitro* Evaluation of Natural Gum-Based Microbeads for Delivery of Ibuprofen

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Abstract

Purpose: *To investigate the effectiveness of three natural gums, namely albizia, cissus and khaya gums, as excipients for the formulation of ibuprofen microbeads.*
Methods: *Ibuprofen microbeads were prepared by the ionotropic gelation method using the natural gums and their blends with sodium alginate at various concentrations using different chelating agents (calcium chloride, zinc chloride, calcium acetate and zinc acetate) at different concentrations. Microbeads were assessed using SEM, swelling characteristics, drug entrapment efficiencies, release properties and drug release kinetics.*
Results: *The natural gums alone could not form stable microbeads in the different chelating agents. Stable small spherical discrete microbeads with particle size of 1.35 ± 0.11 to 1.78 ± 0.11 mm, were obtained using the blends of natural gum: alginate at total polymer concentration of 2 % w/v using 10 % w/v calcium chloride solution at a stirring speed of 300 rpm. The encapsulation efficiencies of the microbeads ranged from 35.3 to 79.8 % and dissolution times, t_{15} and t_{80} increased with increase in the concentration of the natural gums present in the blends. Controlled release was obtained for over 4 h and the release was found to be by a combination of diffusion and erosion mechanisms from spherical formulations.*
Conclusion: *The three natural gums would be useful in the formulation of ibuprofen microbeads and the type and concentration of natural gum in the polymer blend can be used to modulate the release properties of the microbeads.*

Keywords: *Microbeads, Ibuprofen, Natural gums, Sodium alginate, Drug release kinetics*

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INTRODUCTION

Microencapsulation technology offers an alternative way of delivering drugs. Careful consideration of the components of the encapsulation medium not only improves drug solubility but may also facilitate targeted and controlled drug delivery thereby minimizing its side effects and improving pharmacological response [1]. One approach for achieving controlled release of drugs is the production of polymeric gel microbeads which provide a more uniform distribution of drugs within the gastrointestinal tract [2]. In spite of the extensive use of synthetic polymers in the formulation of microbeads, the development of natural biodegradable polymer-based systems for controlled drug delivery continues to be of interest [3]. Biodegradable polymers including natural gums and starches have been utilized as carriers because of their relative availability,

capability for multiple chemical modifications and compatibility [3-5].

Ibuprofen, [±-2, - (4'isobutyl phenyl) propanoic acid] a potent non-steroidal anti-inflammatory drug (NSAID) has antipyretic and analgesic properties [9] but its duration of action is fairly short (1-2 h) making repeated administration necessary during 24 h period [6]. Gastric irritation is a major side effect of ibuprofen, mainly due to the free carboxylic acid in the chemical formula [7]. Ibuprofen also has poor tableting properties due to its hydrophobic-substituted isobutyl benzene and its low solubility in suitable media has limited its formulation development. In addition, its high cohesiveness which result in poor flowability has made its development quite challenging. Previous studies have shown that ibuprofen is capable of being encapsulated as bead formulations using sodium alginate and other natural polymers such as starch [8]. However, initial burst release which is undesirable for controlled release agents has been reported [8].

Thus, in the present study, three natural gums, namely: albizia gum, obtained from the incised trunk of the tree *Albizia zygia* (DC) J.F. Macbr, Family leguminosae, cissus gum, obtained from the stems and roots of *Cissus pulpunae*, Guill and Perr, Family Ampelidacae, and khaya gum, obtained from the incised trunk of *Khaya grandifoliola* CDC (Meliaceae), have been evaluated as potential carriers for controlled delivery of ibuprofen microbeads. The three natural gums have previously been characterized and found to be useful for controlled delivery of some drugs [9-11]. The main focus of the present study was the formulation of microbeads which will avoid the initial burst release which had previously been reported for ibuprofen using sodium alginate and other polymer blends [8]. The ibuprofen microbeads were prepared by the ionotropic gelation technique and the effects of different gum/alginate ratios on the release properties of the microbeads were evaluated.

EXPERIMENTAL

Materials

The materials used are sodium alginate (Carl Roth GmbH & Co, Germany), calcium chloride (Alfa Aesar GmbH & Co, Karlsruhe, Germany). Albizia and khaya gums were obtained from the incised trunks of *Albizia zygia* and *Khaya grandifoliola* respectively, from the botanical garden, University of Ibadan, Nigeria. Cissus gum was obtained from the stems of *Cissus pulpunea*, from local farmers in Tose village, Nigeria. The collection, purification and characterization of the natural gums have been described elsewhere [5,9]. All other reagents were of analytical grade.

Preformulation studies

Preformulation studies were carried out using different chelating agents in order to optimize the formulation and physicochemical properties of the microbeads. Several formulation trials were carried out using varying concentrations (5, 7.5 and 10 % w/v) of the natural gums alone, different chelating agents (calcium chloride, zinc chloride, calcium acetate and zinc acetate) at different concentrations (10, 15 and 20 % w/v), stirring speed (200, 300 and 400 rpm) and curing times (15, 30 and 60 min). However, the beads formed could not retain their integrity outside the chelating agents. Thus, various polymer blends consisting of the different ratios of natural gums and sodium alginate, type and concentration of cross-linking agent, stirring speed and curing time were used.

Preparation of microbeads

Ibuprofen microbeads were prepared from the hot gel blend (90 ^{o}C) of natural gum and sodium alginate. The gum and sodium alginate were blended to obtain a total polymer concentration of 2 % w/v at gum to sodium alginate ratios of 1:1, 2:1 and 3:1. Appropriate quantity of drug was added such that the ratio of total polymer to drug was 2:1. The resulting dispersion was extruded using a syringe with 0.90 mm needle at a dropping rate of 2 ml/min into calcium chloride solution (10 % w/v) maintained under agitation of 300 rpm) using a magnetic stirrer. The formed beads were allowed 30 min curing time and then left standing for 1 h. The beads were collected by decantation, washed repeatedly with distilled water and then dried for 24 h in hot air oven at 40°C temperature.

Characterization of beads

Size and morphology

The particle sizes of the microbeads were determined using optical microscopy method while the morphology and surface characteristics of the microbeads were analyzed using scanning electron microscopy (Hitachi Model S- 2460N Japan) at an accelerating voltage of 25 KV.

Swellability

For determination of swellability, 100 mg of microbeads was soaked in 20 mL of phosphate

buffer pH 6.8. The microbeads were then removed and excess buffer was wiped using a dry filter paper and their final weight was determined. The swollen microbeads were handled carefully in order to avoid any loss of mass due to erosion. The weight of the beads was determined after 3 h. Swellability was computed as in Eq 1.

Swelling index (%) = (C/I)100 …….. (1)

where C is the weight gain and I is the initial weight of the microbeads

Entrapment efficiency

Ibuprofen microbeads (50 mg) were accurately weighed and crushed in a glass mortar and suspended in 10 mL of phosphate buffer, pH 6.8 with continuous stirring. After 24 h, the solution was filtered. The filtrate was appropriately diluted using phosphate buffer, pH 6.8 and analyzed spectrophotometrically at 225 nm using UV/VIS spectrophotometer (LAMBDA 12, Perkin Elmer GmbH, Germany). Drug entrapment efficiency (E) was calculated as in Eq 2.

E (%) = (A/T)100 …… (2)

where A and T are the actual and theoretical theoretical contents of ibuprofen, respectively.

Drug release study

The drug release behavior of the microbeads was evaluated in 900 mL phosphate buffer, pH 6.8 maintained at 37 ± 0.5 °C using the paddle method (USP XXI) rotated at 50 rpm. Samples (5 ml) were withdrawn at different time intervals and replaced with equal amount of fresh medium. The amount of ibuprofen released was determined at wavelength of 225 nm UV/visible spectrophotometer (UV-LAM 12-00996, Perkin Elmer GmbH, Germany). Determinations were done in triplicates.

Modeling of release profile

Data obtained from *in vitro* release studies were fitted to various kinetic equations to determine the kinetics and mechanism (s) of drug release from the microbeads. The results of the drug release for the formulations was fitted to zero order, first order, Higuchi, Hixon-Crowell, Korsemeyer – Peppas and Hopfenberg equations [12-16]. The model of best fit was identified by comparing the values of correlation coefficients.

Data analysis

Each experiment was conducted in quadruplicate and the mean determined. Statistical analysis was carried out using the analysis of variance (ANOVA) on GraphPad Prism© 4.0 (Graphpad Software Inc. San Diego, CA, USA) to compare the differences between formulations. $P \leq 0.05$ was considered significant.

RESULTS

Preformulation profile

The result of the preliminary formulation studies showed that the natural gums alone could not form microbeads with the cross linking agents at different concentration except at 20 % w/v calcium chloride and zinc chloride. The beads were non-spherical and could not retain their integrity outside the cross-linking agent even when the curing time was increased to 1 h. However, when the natural gums were mixed with sodium alginate at ratios of gum:alginate of 4:1, 3:1, 2:1 and 1:1 to produce total polymer concentrations of 1, 2 and 4 % w/v, rigid spherical microbeads were formed at total polymer concentration of 2 % w/v at ratios of 3:1, 2:1 and 1:1 using only calcium chloride as the chelating agent. The results showed that the most spherical and stable microbeads were obtained from polymer blends of the natural gum and sodium alginate at concentration of 2 % w/v using calcium chloride (10 % w/v) as cross-linking agent at the stirring speeds of 300 rpm. The detailed compositions of the optimized microbeads are shown in Table 1.

Physicochemical properties of the microbeads

The results show that the yield of the microbeads collected after drying was 90 – 94 % w/w. The scanning electron micrographs of the ibuprofen-loaded microbeads are presented in Figure 1 while the properties of the optimized microbeads are presented in Table 1. SEM revealed that small spherical microbeads with rough surface morphology were obtained using the natural gums and sodium alginate blends. The mean particle sizes of the beads after drying ranged from 1.25 ± 0.11 to 1.78 ± 0.11 mm. The size of the microbeads increased with increase in the concentration of the natural gum present in the polymer blend. The ranking of the bead size was formulation containing khaya > albizia > cissus > alginate alone. The microbead formulation containing khaya gum generally exhibited higher

bead size while those containing alginate alone showed the smallest bead size. However, there are no statistically significant (p > 0.05) difference in the size of the microbeads prepared using the different polymers.

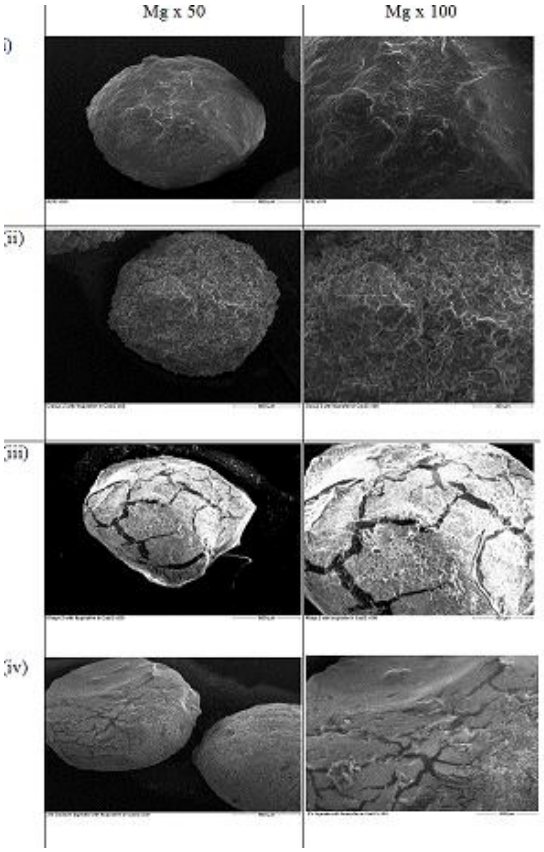

Figure 1: Scanning Electron Micrographs of Ibuprofen-loaded microbeads containing the natural gum: alginate at ratio of 3:1: (i) albizia-alginate; (ii) cissus-alginate; (iii) khaya-alginate; (iv) 2 % sodium alginate; magnification: 50 and 100

The results of the swelling index of the beads shown in Table 1 indicates that the swelling index generally decrease with increase in the concentration of the natural gum present in the polymer blends. The ranking of the swelling index was formulations containing alginate > khaya > cissus > albizia.

The encapsulation efficiencies of the microbeads also presented in Table 1 were found to range from 35.3 to 79.8 %. The ranking for the entrapment efficiency was formulation containing albizia > alginate > cissus > khaya. Formulations containing khaya gum exhibited significantly lower (p < 0.05) entrapment efficiency than those containing the other polymers.

Drug release

The release profiles of ibuprofen from the microbeads are shown in Figure 3 while the dissolution times, t_{15} and t_{80}, (time for 15 and 80 % drug release respectively) are presented in Table 1. The drug release profiles from the microbeads were characterized by an initial lag phase where slow drug release was observed before the drug release rate became faster. This indicated that the drug was embedded in the polymeric matrix. The dissolution times generally increased with increase in the concentration of natural gum in the formulation in the rank order of formulation containing alginate > albizia > cissus > khaya. The dissolution time, t_{80}, of microbeads containing khaya gum was significantly (p < 0.05) lower than those containing the other natural gums especially at lower concentrations.

Table 1: Properties of ibuprofen microbeads containing the natural gums and sodium alginate (mean ± SD, n = 3)

Polymer matrix	Polymer ratio	Particle size (mm)	Swellability (%)	Entrapment efficiency (%)	t_{15} (h)	t_{80} (h)
Alginate		1.25 ± 0.11	16.9 ± 1.4	58.4 ± 3.5	1.6 ± 0.1	3.7 ± 0.6
Albizia: alginate	1:1	1.36 ± 0.11	9.2 ± 0.5	59.3 ± 3.5	1.2 ± 0.3	3.0 ± 0.4
	2:1	1.49 ± 0.16	7.6 ± 1.2	79.8 ± 1.6	1.5 ± 0.1	3.4 ± 0.3
	3:1	1.71 ± 0.18	7.0 ± 0.9	52.5 ± 4.3	1.5 ± 0.2	3.6 ± 0.5
Cissus: alginate	1:1	1.14 ± 0.11	16.6 ± 0.6	50.5 ± 3.5	1.1 ± 0.2	2.7 ± 0.4
	2:1	1.34 ± 0.16	11.6 ± 1.4	68.5 ± 4.0	1.3 ± 0.2	3.0 ± 0.4
	3:1	1.46 ± 0.14	9.4 ± 0.7	51.3 ± 3.5	1.8 ± 0.2	3.8 ± 0.3
Khaya: alginate	1:1	1.47 ± 0.12	16.8 ± 1.3	35.3 ± 4.2	0.9 ± 0.1	1.9 ± 0.2
	2:1	1.64 ± 0.10	11.8 ± 1.1	38.8 ± 1.9	0.9 ± 0.1	2.0 ± 0.4
	3:1	1.78 ± 0.11	10.2 ± 1.1	38.3 ± 1.6	1.2 ± 0.1	3.1 ± 0.4

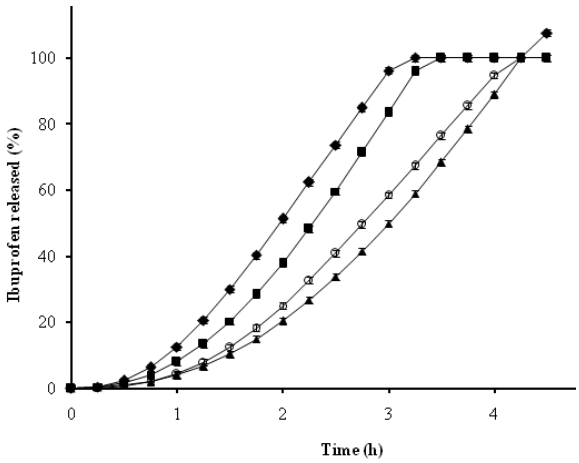

Figure 2: Dissolution profile of ibuprofen-loaded microbeads containing cissus gum : alginate blends at ratio of ◆, 1:1; ■, 2:1; ▲, 3:1 and ●, sodium alginate alone (mean ± SD, n=3)

The correlation coefficients which were used as an indicator for best fit into the drug release kinetics are presented in Table 2. The results showed that drug release from the microbeads containing all the polymer blends fitted the Korsmeyer-Peppas and the Hixson-Crowell models with correlation coefficients, r2 ≥ 0.992.

DISCUSSION

The preliminary formulation studies showed that the natural gums could not form stable spherical microbeads outside the chelating agent. This could be because the natural gums do not contain sufficient quantities of substrate which are required to build the structural entity as it is the case with sodium alginate. Polymer concentration of 1 % w/v, appeared to be too dilute to form rigid, spherical beads while the concentration of 4 % w/v was too viscous for easy extrusion through the 0.90 mm diameter needle. Furthermore, polymer blended at the ratio of gum to sodium alginate of 4:1 did not form well defined microbeads. Thus, the total polymer concentration of 2 % w/w was used for further formulation studies.

The preformulation studies also showed that at the stirring speeds of 200 rpm, the microbeads were generally irregular in shape but became more spherical at the stirring speed was increased to 300 rpm. However, when the stirring speed was increased to 400 rpm, the beads became more irregular in shape. When the cross linking agents - calcium chloride, zinc chloride calcium acetate and zinc acetate were used at the concentration of 5.0, 7.5 and 10.0 % w/v, varying degrees of cross linking was obtained with only calcium chloride at a concentration of 10 % w/v producing the most spherical and stable microbeads. It has been reported that divalent calcium cations bind preferentially to the polyguluronic acid units (GG) of alginate in a planar two-dimensional manner, producing the so-called ‘‘egg-box’’ structure [17]. Different cations such as Ca^{2+}, Zn^{2+}, Ba^{2+} and Sr^{2+} have been reported to bind at different sites of the alginate molecule to form stable bioadhesive gel [18].

The curing time was also found to affect the quality of the microbeads. The curing time of 30 min produced more spherical and free-flowing beads. Furthermore, it was observed that when the microbeads were left standing for one hour after curing, the microbeads were more stable and did not disintegrate during the recovery. This indicates that keeping the microbeads in the cross linking agent for a period of time allowed for further cross linking to occur in the gel.

Table 2: Correlation coefficient obtained for the ibuprofen microbeads using different kinetic models (n = 3)

Polymer	Polymer ratio	Zero order	First order	Higuchi	Hixson-Crowell	Korsmeyer	
						r^2	n
Alginate		0.9562	0.8356	0.7673	0.9952	0.9972*	2.439
Albizia-alginate	1:1	0.9742	0.6532	0.8152	0.9993*	0.9933	1.802
	2:1	0.9480	0.8200	0.7778	0.9964	0.9993*	2.430
	3:1	0.9474	0.8391	0.7938	0.9964*	0.9908	2.078
Cissus-alginate	1:1	0.9678	0.7144	0.9130	0.9992*	0.9944	1.808
	2:1	0.9557	0.6943	0.7611	0.9938	0.9989*	2.188
	3:1	0.9200	0.8456	0.7472	0.9892	0.9981*	2.236
Khaya-alginate	1:1	0.9061	0.7757	0.7423	0.9994*	0.9950	2.064
	2:1	0.8731	0.7810	0.7303	0.9978*	0.9974	2.197
	3:1	0.9763	0.9060	0.8557	0.9923*	0.9893	1.665

**Highest correlation coefficient of drug release kinetics*

The yield of the microbead collected after drying was greater than 90 % indicating high recovery and the suitability of the polymer blends for the formulation of microbeads. The scanning electron micrographs revealed that small spherical microbeads with rough surface morphology similar to those obtained in previous studies using other natural gums were obtained [5]. The size of the microbeads were found to depend on the type and concentration of natural gum present in the polymer blends. The results of the swelling index of the beads showed that there was a gradual increase in the size of the beads with time (data not shown). However, the swelling reached its maximum value at 3 h, after which erosion and breakdown of the beads began to occur which has been attributed to a breakdown in the polymeric backbone of the microbeads into fragments which results in the disintegration of the microbeads [5]. The swelling index generally decreased with increase in the concentration of the natural gum present in the polymer blends with formulations containing alginate alone showing the highest swelling index and those containing albizia gum showing the lowest values. The swelling properties of the microbeads depended on the type and concentration of natural gum present in the polymer blend which could be attributed to the difference in their crystallinity and degree of cross linking of the local gums [5].

The entrapment efficiency increased with increase in the concentration of the natural gum from ratio 1:1 to 2:1 but decreased at ratio 3:1 with formulations containing albizia gum showing the highest values and those containing khaya gum the lowest values. Previous studies have reported a decrease in the viscosity of the polymer blend with increase in the concentration of the natural gum in the polymer blend [5]. Thus, at ratio 3:1, the polymer is less viscous which could facilitate faster diffusion of the drug out of the polymeric matrix of the microbeads leading to lower encapsulation efficiency. Thus, the polymer to alginate ratio of 2:1 gave the highest entrapment efficiency.

For controlled release preparations, an initial high rate of drug release usually referred to as “burst release” where 15 % of drug is released within the first hour, is undesirable due the potential adverse pharmacological effects which could also render the delivery system more economically ineffective [19]. The time for 15 % drug release, t_{15}, was found to be greater than one hour except for the formulations containing lower concentrations of khaya gum where the t_{15} values were less than 1 h. The values t_{15} depended on the type and concentration of natural gum in the polymer blend. Thus, the polymer blend of the natural gums (cissus and albizia) and sodium alginate could be suitable in preventing the burst release in microbead formulations. The result of the dissolution times showed that the concentration of the natural gum in the bead formulation could be used to modulate the dissolution properties from the microbead formulations. Furthermore, the results showed that the bead size and the dissolution times of ibuprofen microbeads was generally lower than the values previously reported for diclofenac microbeads using the same polymer blends [5]. The difference in the dissolution times may be due to the cracks and fissures observed in the ibuprofen microbeads which were not present in the diclofenac beads. This is probably due to the difference in the nature of the non steroidal anti-inflammatory drug such as the partition coefficient which increases from 3.97 for ibuprofen to 4.51 for diclofenac.

The kinetics of drug release are important due to their influence on drug bioavailability, dosage intervals and occurrence of toxic or untoward side effects [14]. The kinetics of drug release from the microbeads containing all the polymer blends fitted the Korsmeyer-Peppas and Hixson-Crowell models which indicate that drug release from the microbeads was controlled by a combination of diffusion and erosion mechanisms from spherical microbeads with changes in surface area and diameter [5]. Furthermore, the n value indicates that the drug release mechanism from the formulations was by super case II transport, in which a pronounced acceleration in drug release from the microbeads occur toward the latter stages of release, resulting in a more rapid relaxation-controlled transport [20]. This is consistent with previous reports on release kinetics of microbead formulations [5]. The physicochemical properties of drug and polymer as well as the drug to polymer ratio have been shown to govern the release of drug from formulations which could also modify their release kinetics. This indicates that the amount of the gum could be used to modify the release properties of the microbeads.

CONCLUSION

Small discrete microbeads of ibuprofen with high yield values and controlled drug release over a period of 4 h have been obtained. Drug release from the microbeads is altered by the addition of the polymer gums to the formulation and is dependent on the type and amount of natural gum present in the formulation. Thus, the natural

gums tested would be suitable as excipients in combination with sodium alginate for the formulation of microbeads when burst release is not desired, such as in NSAID therapy.

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REFERENCES

1. *Momin M, Pundarikakshudu K. In vivo studies on guar gum based formulation for the colon targeted delivery of sennosides. J Pharm Pharm Sci 2004; 7(3): 325-331.*
2. *Xing L, Dawei C, Liping X, Rongqing Z. Oral colon-specific drug delivery for bee venom peptide: development of a coated calcium alginate gel beads-entrapped liposome. J Control Rel 2003; 93: 293-300.*
3. *Baveja SR, Ranga RKV, Arora J. Examination of natural gums and mucilages as sustaining materials in tablet dosage forms. J Pharm Sci 1989; 51(4): 115-118.*
4. *Zhang J, Xu S, Zhang S, Du Z. Preparation and Characterization of Tamarind Gum/ Sodium Alginate Composite gel beads. Iranian Polym J 2008; 17 (12): 899-906.*
5. *Odeku OA, Lamprecht A, Okunlola A. Characterization and evaluation of four natural gums as polymers in formulations of diclofenac sodium microbeads. Int. J. Biol. Macromol. 2013; 58: 113-120.*
6. *Cox PJ, Khan KA, Munday D, Sujja-areevath J. Development and evaluation of a multiple-unit oral sustained release dosage form from S (+)-ibuprofen: preparation and release kinetics. Int J Pharm. 1999; 193: 74–84.*
7. *Gilman AG, Goodman LS, Rall TW, Murad F. The pharmacological basis of therapeutics. 7th ed. New York. Macmillan Publishing Company. 1985. 943p*
8. *Rasenack N, Muller BW. Ibuprofen crystals with optimized properties Int J Pharm 2002; 245: 9-24.*
9. *Odeku OA, Fell JT. Evaluation of Khaya gum as a directly compressible matrix system for controlled release. J Pharm Pharmacol 2004; 56 (11): 1365-1370.*
10. *Eichie FE, Amalime AE. Evaluation of the binder effects of the gum mucilages of Cissus populnea and Acacia senegal on the mechanical properties of paracetamol tablets. Afr J Biotechnol 2007; 6 (9): 2208-2211.*
11. *Odeku OA. Assessment of Albizia zygia gum as binding agent in tablet formulations. Acta Pharm 2005; 55: 263-276.*
12. *Wagner JG. Interpretation of percent dissolved time plots derived from in vitro testing of conventional tablets and capsules. J Pharm Sci 1969: 58 (10): 1253-1257.*
13. *Gibaldi M, Feldman S. Establishment of sink conditions in dissolution rate determinations - Theoretical considerations and application to non disintegrating dosage forms. J Pharm Sci 1967: 56 (10): 1238-1242.*
14. *Hixson AW, Crowell JH. Dependence of reaction velocity upon surface and agitation. Ind Eng Chem 1931; 23: 923-931.*
15. *Korsemeyer RW, Gurny R, Doelker EM, Buri P, Peppas NA. Mechanism of solute release from porous hydrophilic polymers. Int J Pharm 1983; 15: 25-35.*
16. *Costa P, Lobo JMS. Modeling and comparison of dissolution profiles. Eur J Pharm Sci 2001; 13: 123-133.*
17. *Grant GT, Morris ER, Rees DA, Smith PJ, Thom D. Biological interactions between polysaccharides and divalent cations - the egg-box model. FEBS Lett 1973; 32: 195-198.*
18. *Nayak AK, Hasnain MS, Beg S, Alam MI. Mucoadhesive beads of gliclazide: Design, development and evaluation. Sci Asia 2010; 36: 319-325.*
19. *Huang X, Brazel CS. Importance and mechanisms of burst release in matrix-controlled drug delivery. J Control Rel 2001; 73: 121-136.*
20. *Jacques CHM, Hopfenberg HB. Stannett V. Super case II transport of organic vapors in glassypolymers. In: Hopfenberger HB (Ed). Permeability of plastic films and coatings to gases, vapors, and liquids. Plenum Press, New York. 1974; pp73-86.*