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Influence of some channeling agents on the release profile of Khaya Ivorensis - Ibuprofen matrix tablets

***[1]Uhumwangho M.U., [1] Iwuagwu C .E and [2]Latha K**

[1]Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, University of Benin, Nigeria
[2] G. Pulla Reddy College of Pharmacy, Mehidipatnam, Hyderabad, India

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ABSTRACT

The study was carried out to investigate the effect of channeling agents (sodium chloride or mannitol) on the release profiles of ibuprofen-matrix tablets formulated with a natural gum. Ibuprofen matrix granules were formed by wet granulation technique using khaya gum (15%w/w). Different channeling agents at varying concentrations were incorporated. Magnesium stearate (0.5%w/w) was incorporated into the ibuprofen-matrix granules prior to compression at a compression load of 30 (arbitrary unit on the load scale). Granules were evaluated for micromeritic properties while the formulated tablets were evaluated for tablet crushing strength, friability and in-vitro dissolution studies. The release data were subject to different release kinetics and their release mechanism was studied. All granules were free flowing with angle of repose $\leq 31^0$. The densities were not affected by the presence of any of the channeling agents. Generally, the dissolution rate increased with increase in concentration of the channeling agents. The influence was slightly more with sodium chloride compared with mannitol. For instance, the dissolution rate (m_∞/t_∞) without channeling agents and with channeling agents at same concentration (200mg) were $3.59\%h^{-1}$ (without channeling agent), $6.04\%h^{-1}$ (with mannitol as channeling agent) and $7.76\%h^{-1}$ (with sodium chloride as channeling agent. The mechanism of drug release from these formulations followed anomalous transport, often termed as first-order release since the diffusional release exponent (n) for all the formulations was between 0.45 and 0.89. The presence of channeling agents influenced the release of drugs from the matrix system studied. Therefore; controlled amount as well as appropriate channeling agents can be used to enhance and modulate the release of drugs from such systems studied.

Keywords: Khaya gum, channeling agents, ibuprofen, release kinetics

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INTRODUCTION

Controlled release (CR) formulations are designed to deliver drugs at a predetermined rate over a wide range of conditions and duration of therapeutic treatment. In the past few decades, CR dosage forms have made tremendous progress in terms of clinical efficacy and patient compliance [1]. Matrix-based systems are non disintegrating systems, which are used in the manufacture of CR devices. Matrix system is commonly used for manufacturing CR dosage forms due to its ease of manufacture [2].

Different polymers have been explored in the designed of CR formulations. Most of them are synthetic hydrophilic polymers while others can be natural polymers. Khaya gum is a natural polymer, obtained as exudates from *Khaya*

ivorensis tree of the family Meliaceae. Khaya gum has been evaluated as a CR agent in modified release matrices in comparison with hydroxypropylmethylcellulose (HPMC) using paracetamol (water soluble) and indometacin (water insoluble) as model drugs [3] but the influence of channeling agents (Sodium chloride or mannitol) was not investigated. Previously, some researchers have investigated the use of some channeling agents to control drug release from a matrix core formed with an inert polymer, Eudragit RS100 [4].

Ibuprofen is a nonsteroidal antiinflammatory drug (NSAID). It is a white to off-white crystalline powder, with a melting point of 75° to 77°C, practically insoluble in water (< 0.1 mg/mL). The chemical name for ibuprofen is (±)-2-p- sobutylhydratropic acid and its molecular weight is 206.28. It has analgesic, antipyretic and anti inflammatory properties hence, is indicated in the treatment of rheumatoid arthritis, osteoarthritis and dysmenorrhea. Its dose is 400 mg every 6 to 8 hrs for the relief of mild to moderate pain in adults. It has a short biological half life of between 1.8 to 2 h. This was used as the model drug. Hence, the objective of the present study was to investigate the influence of sodium chloride or mannitol as channeling agents on CR matrix tablets of Ibuprofen (water insoluble) using khaya gum as a matrix former.

MATERIALS AND METHODS

Materials

Khaya gum was extracted by the method described previously by Mahmud *et al*., [5] with some modifications It was used as the matrix former in preparing the matrix tablets. Mannitol and sodium chloride (Get-Rid Pharm Pvt, Ltd, Pune, India) were analytical grades and were used as channeling agents in the matrix tablets while magnesium stearate (Qualikems Fine Chemical Pvt Ltd, India) was used as lubricant (0.5% w/w) in the tablet formulation. Ibuprofen powder (Dr Reddy's Laboratories Ltd, India) was selected as the test drug because it has a short biologic half life of 1.8 to 2 h and also poorly soluble in water.

Granulation and tableting:

Ibuprofen powder or admixtures of ibuprofen with channeling agents (mannitol or sodium chloride) were formed by wet granulation method using khaya gum (15%w/w) as matrix former (See table 1). The granules were characterized for micromeritics properties prior to compression into tablets. The granules were compressed using a single punch tableting machine (Manesty Type F3, Liver Poole, England) at constant load (30 arbitrary units on the load scale) to form flat faced tablets of diameter 12.5mm. Prior to compression, 0.5%w/w of magnesium stearate was incorporated to facilitate tablet ejection.

Packing and flow properties of granules:

These were determined by measuring the bulk density (BD) and tapped density (TB) using standard procedures [6]. From the data, compressibility index (CI) values of the granules were calculated as CI = {(TB-BD)/TB} ×100% [7]. The flow properties of the granules was determined by measuring the angle of repose formed when a sample of the granules (40 g) was allowed to fall freely from the stem of a funnel to a horizontal surface [6].

Determination of tablet crushing strength and friability:

The crushing strength of 10 tablets was determined by diametrical compression using the Campbell Electronics hardness tester machine. The friability of 5 tablets was determined by the use an Erweka friabulator (Heusenstamm, Germany). All determinations were done in triplicate and mean results was recorded. The tablets crushing strength-friability ratio was also determined. This was determined by using equ 1

$$CS / F \quad \ldots\ldots\ldots\ldots\ldots\ldots 1$$

where CS is crushing strength and F is friability.

Determination of *in vitro* dissolution studies and rate order kinetics:

The *in vitro* dissolution test was done by method described previously by Uhumwangho *et al* [8]. The dissolution data were analyzed on the basis of zero order, first order rate, Higuchi model and Korsmeyer and Peppas [9]. The kinetic models order equations tested were

Zero order equation: $m = k_0 t$ …….2
First order equation: $\log m_1 = \log m_0 - 0.43 k_1 t$ ……..……3

Higuchi: $m = k_H t^{1/2}$…….… 4
Korsmeyer-peppas model: $\log \%m = \log k_2 + n \log t$ ….....5

where m is the percentage (%) amount of drug released in time t; m_1 is the residual amount (%) of drug in time t; m_0 is the initial amount of drug (100%) at the beginning of the first order release; k_0, k_1, k_H and k_2 are the release rate constants for the zero, first order, the Higuichi models and korsmeyer and peppas dissolution model respectively. The n is the diffusional release exponent that could be used to characterize the different release mechanism. For a tablet having a cylindrical shape, n value below 0.45 indicates Fickian diffusion and n values between 0.45 to 0.89 indicate anomalous transport, often termed as first – order release. If the n values reaches 0.89 or above, the release can be characterized by case II and super case II transport, which mean the drug release rate does no change over time and the drug is released by zero-order mechanism. In this case, the drug release is dominated by the erosion and swelling of the polymer [10]. The correlation coefficient (r) for each rate order was also calculated. The dissolution profile was considered to follow a particular rate order if the r value was ≥ 0.95 [11]. All data obtained were subjected to student t- test ($p < 0.05$) to test for significance of difference**.**

RESULTS AND DISCUSSION

Packing and flow properties of the matrix granules

The results of the packing and flow properties of resulting granules with or without channeling agents are presented in Table 2. The densities were not statistically significantly affected by the presence or absence of any of the channeling agents. It was observed that all matrix granules formulated were free flowing with angle of repose $\leq 31^0$. The CI was between 4.3 to 13% while their hausner ratio was between 1.05 to 1.27, indicating good flow properties of the granules. Therefore, presence or type of channeling agents did not affect the flow property of the granules (See Table 2).

Compaction properties of the formulated tablets

The results of tablets hardness values are presented in table 3. All granules were compressible with hardness values between 613N to 683N. However, it was observed that the presence of channeling agents in the matrix granules increased the tablet hardness. For instance, the hardness values for M0, M1 and M3 formulations containing sodium chloride are 613N, 653 and 685N. More so, the hardness of the tablet also depended on the type of channeling agent used in the formulation. Tablets containing mannitol as channeling agents were harder than tablets containing sodium chloride as channeling agents, although there was no statistically significant difference between their hardness values ($P>0.05$). For instance, the hardness values of M1 tablets containing 50mg of sodium chloride and M4 tablets containing the same quantity of mannitol were 632N and 641N respectively (See table 3). The crushing strength- friability ratio also increased with increase in the content of channeling agents (Table 3). The reason attributable to high increase in tablet hardness values with tablets containing mannitol when compared with sodium chloride might be due to the plastic nature of mannitol. All tablets had friability values ≤0.76% (Table 3).

Drug release profiles of the different tablet formulation

The drug release profiles and dissolution parameter from ibuprofen matrix tablets without and with channeling agents (i.e. sodium chloride or mannitol) are shown in Fig 1 and table 4 respectively. It was observed generally that as the quantity of the channeling agents in the ibuprofen matrix tablet formulation increased there was a general increase in the dissolution profile of the matrix tablets. For instance, the dissolution rates (m_∞/t_∞) for M0 (without channeling agent) and M3 (with sodium chloride as channeling agent) and M6 (with mannitol as channeling agent) were 3.6, 7.7 and 6.0%h^{-1} respectively (See Table 4). The indication is that the presence of channeling agents facilitated the drug release from the matrix system. There was a statistically significant difference between their release profiles with and without channeling agent ($P<0.05$). The possible reason for increase in dissolution rate with formulations with channeling agents compared with those without channeling agent could be that pores were created by the different channeling agents which increased the dissolution rate.

Drug release mechanism

Understanding of the drug release kinetics will provide information on the drug release mechanism. The release data for all the formulations (i.e. without channeling agents, with sodium chloride or mannitol as channeling agents) were analyzed based on zero-order kinetics, first-order kinetics, Higuchi mechanism and Korsmeyer and peppas model to ascertain which release model best fit the system studied [9, 12 - 14]. The values of the correlation coefficients (r) and the release rate constants are presented in table 5. The r - values for all the formulations were between 0.930 to

0.983 (zero order), 0.954 to 0.9650 (first order), 0.952 to 0.994 (Higuchi) and 0.959 to 0.990 (Korsmeyer and Peppas). Hence, all the formulations fit best into Higuchi square root of time since they had r^2 values ≥ 0.95. In order to characterize the release mechanism, the diffusional release exponent was determined. The values of release exponent (n) for all the formulations was between 0.45 to 0.89 (See Table 5). The indication is that release of ibuprofen from these formulations followed anomalous transport, often termed as first-order release [9, 12 – 14].

Table 1: Composition of ibuprofen and channeling agents in the different formulations in mg

Formulation code	Ibuprofen powder	Sodium chloride	Mannitol
M0	400	-	-
M1	400	50	-
M2	400	100	-
M3	400	200	-
M4	400	-	50
M5	400	-	50
M6	400	-	50

Table 2: Packing and flow properties of Ibuprofen matrix granules prepared using khaya gum as binder with sodium chloride and mannitol as channeling agents.

Formulation code	Bulk Density(g/cm^3)	Tap Density(g/cm^3)	Angle of repose (θ)	Carr index	Hausner's ratio
M0	0.4780	0.5016	28.35	4.70	1.05
M1	0.4882	0.5615	29.53	13.1	1.15
M2	0.4956	0.5707	30.10	13.2	1.15
M3	0.5493	0.6252	29.42	12.1	1.14
M4	0.4192	0.5252	30.15	20.2	1.25
M5	0.4586	0.5826	31.23	21.3	1.27
M6	0.4942	0.5164	30.56	4.29	1.04

Table 3: Effect of channeling agents (sodium chloride or mannitol) on the hardness and friability of resulting tablets formulated with khaya gum.

Tableting parameters	M0	M1	M2	M3	M4	M5	M6
Crushing strength (N)	613	632	653	685	641	665	683
Friability (%)	0.66	0.71	0.64	0.42	0.76	0.51	0.48
Crushing strength -friability ratio	929	890	1020	1631	843	1303	1422

Table 4: Release parameters {m_∞ (%), t_∞ (h), m_∞/t_∞(%h^{-1})} of the different formulations

Tableting parameters	M0	M1	M2	M3	M4	M5	M6
m_∞ (%)	35.9	46.5	59.7	77.6	38.9	51.9	60.4
t_∞ (h)	10	10	10	10	10	10	10
m_∞/t_∞ (%h^{-1})	3.59	4.65	5.97	7.76	3.8	5.19	6.04

Note: Where m_∞ (%), t_∞(h), and m_∞/t_∞(%h^{-1}) are maximum release, time to attain maximum release and dissolution rate respectively.

Table 5: Correlation coefficient (r) and release kinetics of the different formulations. Data analysed according to zero order, first order, Higuchi and Korsmeyer, and Peppas models.

Formulation code	Zero order		First order		Higuchi		Korsmeyer and Peppas	
	r	K_0	r	K_1	r	K_H	R	n
M0	0.935	3.33	0.960	- 0.02	0.991	11.4	0.959	0.65
M1	0.949	4.49	0.978	- 0.03	0.994	15.4	0.985	0.65
M2	0.978	5.32	0.979	- 0.03	0.974	17.8	0.990	0.56
M3	0.983	7.31	0.965	- 0.06	0.952	24.0	0.966	0.58
M4	0.930	3.89	0.954	- 0.02	0.987	13.4	0.985	0.66
M5	0.962	4.88	0.987	- 0.03	0.992	16.6	0.990	0.65
M6	0.980	5.54	0.977	- 0.04	0.971	17.8	0.983	0.56

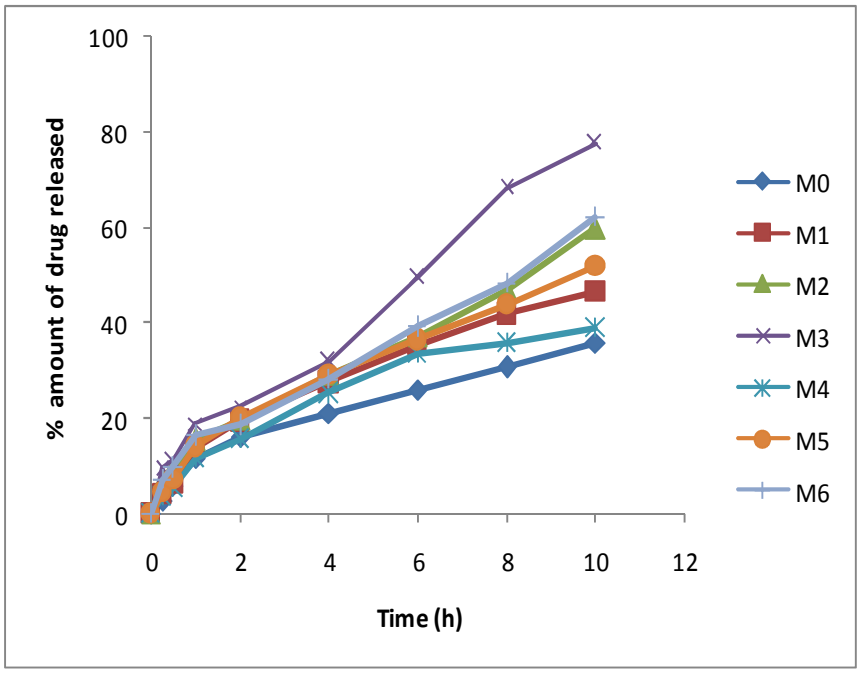

Figure 1: Influence of different channeling agents on the drug release profile of ibuprofen matrix tablets prepared with 15%w/w khaya gum.

CONCLUSION

The presence of channeling agents influenced the release of drugs from the matrix system studied. Therefore; controlled amount as well as appropriate channeling agents can be used to enhance and modulate the release of drugs from such matrix systems.

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