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EVALUATION OF PLANTAGO SEED HUSKS IN COMBINATION WITH OTHER SWELLABLE POLYMERS FOR THE PRODUCTION OF SUSTAINED RELEASE TABLETS.

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ABSTRACT :

In a previous study, plantago ovata husks (PO) were evaluated as a swellable hydrophilic matrix for producing aminophylline sustained release tablets. In this investigation PO combination with either hydroxypropylmethylcellulose (HPMC) or sodium carboxy-methylcellulose (NaCMC), the most widely used hydrophilic matrices were utilized for producing aminophylline sustained release tablets using Avicel, anhydrous lactose, StaRx or Emcompress as direct compression vehicle. All the produced tablet formulations showed acceptable physical properties in agreement with the USP/NF(1995) requirements. The tensile strength of HPMC including tablets was higher than those of NaCMC, especially when using Avicel or anhydrous lactose as excipients. Generally, PO combination with NaCMC produced more sustaining properties than with HPMC. However, no significant difference in release rates could be observed upon using different types of direct compression excipients neither with HPMC nor with NaCMC. The release kinetics study of the prepared tablets revealed that it depends on the type of direct compression vehicle used. Formulations containing anhydrous lactose or StaRx release drug through simple Fikian diffusion, i.e. square root of time versus % released correlation, while zero-order, non Fikian mechanism could be observed in those including Avicel or Emcompress in their formulation.

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INTRODUCTION :

The use of hydrophilic matrix system has attracted considerable attention in recent years for the production of sustained release devices. Cellulose derivatives are the most commonly used hydrophilic polymers for oral sustained-release tablets. Hydroxypropyl-methylcellulose (HPMC) and Sodium carboxy methylcellulose (NaCMC) are the most commonly used members of this group either alone [1-7] or in combination [8-11]. Mixtures of HPMC and NaCMC have proved constant rate of release (zeroorder) [8,10,11].

Plantago ovata (PO) seed husks, which is commonly used as a demulcent, a human serum cholesterol reducing agent and in weight management [12], have been evaluated as a mucilage for pharmaceutical use [13] or as a swellable substance for the production of aminophylline controlled-release matrix tablets [14].

The aim of this investigation is to evaluate plantago ovata in combination with the well known HPMC or NaCMC for producing sustained release aminophylline tablets, and to study the physical properties and the release characteristics of these tablets.

EXPERIMENTAL :

Materials:

Plantago ovata, Psyllium husks, Sat Isabgol, MFRS, India. Anhydrous lactose, anhydrous aminophylline and StaRx: are gifts from the United Pharmaceutical Co., Amman, Jordan. Avicel PH 101 : FMC corporation USA. Emcompress: calcium dihydrogen phosphate. Hydroxypropylmethylcellulose [HPMC], Methocel K100M, Ltd., Orpington, UK. Sodium carboxymethylcellulose[NaCMC], BDH Chemicals Ltd., Poole, UK.

Methods:

Aminophylline tablets were prepared using the formula shown in table 1. This formula was selected depending on the previous investigation [13]. The ingredients were mixed in a cubic mixer (Erweka, Turbula System S27, Germany) after passing through 125-mesh screen. The mixture was compressed into 0.4 gm flat tablets (13 mm in diameter) using Korsch (EK/O, Germany), constant rate tableting machine was adjusted to obtain tablets of hardness between 90 and 120 Newton in every case.

Evaluation of tablets:

Uniformity of weight:

Twenty tablets taken randomly were weighed individually and the average weight, the standard deviation and the coefficient of variation percent (C.V.%) were calculated.

Uniformity of drug content:

The drug (aminophylline) content was determined spectrophotometrically for ten tablets, taken randomly, at 270 nm after extraction individually by water from a crushed tablet. The average of drug content and the coefficient of variation was calculated for each formula. Each formula were tested according to USP/NF(1995) requirements (i.e.±15%)

Table (1): Composition of tablets.

Formula symbol	Aminophylline (mg)	Gelling agent (mg)			Direct compression vehicles(mg)				Talc(mg)
		Plantago	HPMC	NaCMC	Avicel	Emcompress	StaRx	Lactose	
A1	200	50	50	-	96	-	-	-	4
A2	200	50	50	-	-	96	-	-	4
A3	200	50	50	-	-	-	96	-	4
A4	200	50	50	-	-	-	-	96	4
B1	200	50	-	50	96	-	-	-	4
B2	200	50	-	50	-	96	-	-	4
B3	200	50	-	50	-	-	96	-	4
B4	200	50	-	50	-	-	-	96	4

Uniformity of diameter and thickness:

The diameter and thickness of twenty tablets were measured individually using Erweka TBH30 hardness tester and the average and C.V. percent were calculated.

Tensile strength:

The tensile strength (TS) was calculated from the equation:

$$TS = 2H / \pi TD \quad \ldots\ldots (1)$$

Where: "T" is the thickness, "H" is the hardness (or crushing strength) and "D" is the diameter of the tablets.

The hardness of ten tablets selected randomly from each batch was determined using an Erweka TBH30 hardness tester.

Friability :

The percentage weight loss was determined after rotation of twenty pre-weighed tablets for 4 min. at 25 rpm. using an Erweka Friabilator TAR20.

Disintegration time:

The average of time required for the disintegration of 6 tablets was also determined using Pharma Test Disintegrator, Italy.

Dissolution studies:

A USP/NF(23) Hanson dissolution apparatus with six baskets was employed for this purpose. One tablet was placed in each basket, rotating at 100 rpm in 900 ml of the dissolution medium (0.1 N HCI, pH 1.2) at 37°C, and also in pH 6.8 buffer medium. The experiment was run for 10 hours, during which samples were withdrawn, at suitable time intervals, and replaced, by equal volumes of dissolution medium kept at 37°C. Samples were assayed spectrophotometrically, after appropriate dilution, at 270 nm for anhydrous aminophylline.

Viscosity determination :

Different concentrations (0.25, 0.5 and 0.75) from each swellable material used (PO, NaCMC and HPMC) were dissolved in distilled water, and the viscosity values of each were

determined using Rion VT-03 Japan viscometer.

RESULTS AND DISCUSSION

Physical properties:

To produce controlled release Amino-phylline matrix tablets, their flowability is firstly studied by determining the Hausner Factor (HF), and the Carr's Index (CI) from the fluffy and tapped bulk density (Table 2). The flowability of AP was found to be 1.46 HF i.e. very poor. Moreover the flowability of some chosen direct compression vehicles were determined (Table 2) and were found to be of excellent flowability (about 1.1 HF). Upon mixing each of such excipients with AP, a decreasing of HF with increasing CI values could be observed especially with Avicel and Lactose, indicating the improvement of flowability (Table 3). This may subsequently facilitate the tablet production process, because it was very difficult to compress AP powder into tablets neither alone nor with plantago and HPMC or NaCMC.

All the produced tablets were found to be successfully fulfill the USP/NF(1995) requirements with respect to the uniformity of weight and diameter, as well as the friability values (less than 1% in all cases), (Table 4). The tensile strength Ts of the tablets was also acceptable. The uniformity of drug content were also, acceptable according to USP requirements (Table 4).

It could be observed that Avicel and lactose produced harder tablets than the other two excipients. This may be due to their higher flowability. Also, tablets containing HPMC showed higher tensile strength than NaCMC in all cases, confirming similar results obtained by Abdel-Rahman et. al [11].

Release Characteristics:

In a previous study we could state that the plantago ovata seed husks is efficient swellable substance for the production of controlled release aminophylline tablets. The effect of plantago combination with HPMC or NaCMC, the most widely used swellable polymers, on the release characteristics of aminophylline tablets revealed that; all the produced tablets showed pronounced controlled release proper-ties (Fig. 1,2 and table 5). When combined with NaCMC, plantago showed more sustaining properties than with HPMC, which may be attributed to the higher viscosity values produced by NaCMC inclusion compared to HPMC (Table 6). The influence of viscosity had also been studied by Vasquez [16]. However no significant difference in release rate upon using different types of directcompression vehicles neither with HPMC nor NaCMC. These results confirm the findings of Ford et. al [4] who stated that the inclusion of either lactose or calcium phosphate increased the dissolution rate of HPMC matrices with no significant difference.

Table(2): The flowability of aminophylline and the direct compression excipients.

Parameters	Aminophylline	Avicel	Emcopress	StaRx	Anh.Lactose
Hausner's Factor(HF)	1.46	1.13	1.11	1.08	1.13

Carr's Index	31.60	11.11	9.66	7.68	11.11

Table (3): Flowability of the mixed formulations before tabletting.

Parameters	Plantago & HPMC				Plantago & NaCMC			
	Avicel	Emcopress	StaRx	Lactose	Avicel	Emcopress	StaRx	Lactose
Hausner's Factor	1.20	1.36	1.33	1.17	1.28	1.38	1.36	1.15
Carr'sIndex	16.64	26.33	24.97	14.29	22.13	27.7	26.33	13.38

Table (4): Physical Properties of the prepared aminophylline tablets.

Parameters	Plantago & HPMC				Plantago & NaCMC			
	Avicel	Emcopress	StaRx	Lactose	Avicel	Emcopress	StaRx	Lactose
Uniformity of weight (g)	0.4120 (3.979)	0.437 (2.073)	0.4066 (1.734)	0.4018 (1.447)	0.4136 (2.375)	0.4162 (2.010)	0.4015 (1.672)	0.4030 (1.201)
Uniformity of thickness (mm)	2.57 (2.098)	2.42 (0.006)	2.51 (0.731)	2.27 (0.258)	2.46 (0.210)	2.33 (3.250)	2.38 (0.561)	2.33 (0.549)
Uniformity of diameter (mm)	13.03 (0.000)	13.02 (0.000)	13.04 (0.000)	13.17 (0.000)	13.04 (0.000)	13.04 (0.001)	13.04 (0.000)	13.11 (0.000)
Uniformity of drug content (g)	0.2125 (2.153)	0.2268 (1.698)	0.2102 (3.002)	0.1989 (1.203)	0.2006 (1.894)	0.2207 (0.898)	0.1978 (3.152)	0.2117 (2.005)
Tensile strength (N/Cm^2)	192.63 (5.174)	135.44 (3.532)	160.94 (2.722)	198.47 (2.929)	139.40 (1.668)	113.83 (7.428)	114.93 (6.144)	119.68 (3.901)
Friability value	0.145	0.322	0.156	0.420	0.304	0.344	0.578	0.764

Table (5): Release kinetics of the prepared aminophylline tablets.

Swellable excipients	Direct compression vehicle	"n"(1)	r(2)	K(3)	t_{50} (4)
Plantago & HPMC	Avicel	0.710	0.994	1.637	123.02
	Emcompress	0.602	0.998	0.400	141.25
	StaRx	0.474	0.990	4.457	164.06
	Lactose	0.531	0.997	4.217	105.44
Plantago & NaCMC	Avicel	0.881	0.986	0.392	245.47
	Emcompress	0.905	0.997	0.279	309.30
	StaRx	0.531	0.994	3.589	145.21
	Lactose	0.647	0.996	1.493	227.51

(1)"n" : Exponent of drug release.
(2) r : Correlation coefficient.
(3) K : Kinetics constant.
(4) t_{50} : Time required to release 50% of the drug.

Table (6): The viscosity values of the swellable materials used at different concentrations.

Swellable material	Concentration		
	0.25	0.50	0.75
PO	3.2	14.9	28.2
NaCMC	4.0	5.4	5.6
HPMC	2.4	2.9	3.5

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Fig. (1) : Dissolution profiles of aminophylline tables containing palantago and HPMC with different excipients .

Fig. (2) : Dissolution profiles of aminophylline tables containing palantago and NaCMC with different excipients .

To describe the general solute release behavior from controlled release polymer matrices; Korsmeyer [17] used a simple equation:

$$M_t / M_\infty = Kt^n \quad \text{..... (1)}$$

Where: M_t / M_∞ = Fraction of drug released at time "t", K=Kinetic constant, and n=diffusion exponent of drug release.

Ford [4] simplify and rewritten equation (1) as:

$$Q=Kt^n \quad \text{..... (2)}$$

Where Q= the percent of drug released . Thus; the logarithmic form of equation (2) is:

$$\text{Log } Q = \text{Log } k + n\text{Log } t \quad \text{..... (3)}$$

From which values of (n) where determined.

Upon studying the release kinetics of the prepared tablets, depending on the "n" values, it could be observed from Fig (1,2) and table 5 that the release of AP from tablets containing HPMC with plantago was according to Higuchi mechanism, ($n \approx 0.5$) i.e. simple Fickian diffusion, except for Avicel containing formula ($n=0.7$) which showed zero-order, non Fickian mechanism. However, form-ulations of NaCMC and plantago showed Fikian diffusion release only with StaRx and lactose ($n \approx 0.5$), while Emcompress and Avicel inclusion render the tablets to release drug according to zero-order kinetics ($n=0.9$) i.e. non-Fickian mechanism. This may be attributed to the insolubility of the latter two diluents. They also showed slower release (t_{50} of 245 and 309 min. respectively) compared to the other two diluents.

CONCLUSION :

From the previous results it could be concluded that plantago ovata seed husks combination with HPMC or NaCMC produced controlled aminophylline tablets with acceptable physical properties. Its combination with NaCMC produced more sustaining effect than with HPMC. However, no significant difference in release rates upon using different types of direct compression vehicles neither with HPMC nor NaCMC.

Tablets containing lactose or StaRx release drug through simple Fickian diffusion (T correlation), while zero-order, non-Fickian mechanism could be observed in those including Avicel or Emcompress.

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تقييم قشور بذور نبات حب البرغوث بالاشتراك مع مبلمرات انتفاخية لإنتاج أقراص ممتدة المفعول

عادل محمد على

لقد تم فى بحث سابق تقييم قشور نبات حب البرغوث كقوالب مائية انتفاخية لإنتاج أقراص أمينو فيللين ممتدة المفعول .أما في هذا البحث فقد تم تقييم استخدامها مختلطة مع " هيدروكس بروبيل ميثيل السليولوز (هـ . س) " وأيضاً مع كربوكس ميثيل سليولوزات الصوديوم (ك.ص) _وهي أكثر القوالب المائية الانتفاخية استخداماً لهذا الغرض - لإنتاج أقراص أمينو فيللين ممتدة المفعول بطريقة الكبس المباشر باستعمال "الأفيسيل" و"اللاكتوز اللامائى" و"الستاركس" و"الإمكومبرس". وقد أظهرت النتائج أن الأقراص المحضرة لها صفات فيزيائية مقبولة طبقاً لمواصفات دستور الأدوية الأمريكي سنة ١٩٩٥ . وأن الأقراص المستخدم فيها مادة (هـ.س) لها قوة تحمل للضغط أكثر من تلك التي استخدم فيها مادة (ك .ص) خاصة عند استخدام "الأفيسيل" واللاكتوز اللامائى وعموماً فقد وجد أن خلط قشور بذور نبات حب البرغوث مع مادة (ك. ص) يعطي امتداد للمفعول أكثر من خلطها مع مادة (هـ.س) . بينما اختلاف غير ملحوظ فى سرعة انطلاق الدواء من الأقراص باستخدام الأنواع المختلفة من مواد الكبس المباشر لا فى وجود (ك.ص) ولا (هـ.س) .أما عن دراسة ديناميكية انطلاق الدواء من الأقراص فقد اتضح أنها تعتمد على نوع مادة الكبس المباشر المستخدمة ؛ فالأقراص التي تحتوى على اللاكتوز اللامائي والستاركس تعتمد على معادلة الانتشار (نسبة الدواء المنطلق تتناسب مع الجذر التربيعى لوقت الانطلاق) . بينما تلك التى تحتوي على "الأفيسيل" و"الإمكومبريس" فكان انطلاق الدواء يعتمد على معادلة "درجة الصفر" أى أن انطلاق الدواء يتناسب مباشرة مع وقت الانطلاق.