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Original Article

FORMULATION AND EVALUATION OF SUSTAINED RELEASE TABLETS OF PENTOXIFYLLINE USING OKRA EXTRACT AS A NOVEL RETARDANT

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ABSTRACT

Objectives: Okra (*Abelmoschus Esculentus*) is one of the world wide distributed plants used mostly as a food in most civilizations, its fruit characterized by sticky materials tears from it upon fruit cutting, this sticky material could be beneficial in matrix formation and sustained release tablets formulation.

Methods: Fresh okra was collected and macerated in different extracting systems in variable ratios. The extracts were dried and collected. Selected extracts were granulated and compressed into tablets using the tablet machine. The formulated tablets were characterized in terms of hardness, friability disintegration and other gross findings, Extract from HCl and NaoH (OE $_{7 \text{ and } 8)}$ were selected to prepare SR tablet of pentoxifylline (PTX); the same tests were performed in addition to measure the rate of PTX release from the tablet over ten hours.

Results: Results obtained shows a promising retardation polymer as the tablets has an elegant shape and texture without chips or cracks, and not friable (F_{HCl} 1 loses 0.03 % of its weight after friability testing), tablet strength is acceptable since tablets resist breaking strength more than 200 Newtons, in addition, time needed for tablet disintegration about 175 minutes as found in F $_{NaoH}$ 3. Fortunately, the prepared tablets show a slow release of PTX following zero order kinetic (90 % released in eight hours in a constant rate about 10% per hour).

Conclusions: These results show the emerging of novel retardant for SR preparation obtained from natural plant okra.

Keywords: Plant extract, Okra, *Abelmoschus esculentus*, Sustained Release, Pentoxifylline, CMC.

INTRODUCTION

Plant kingdom is rich in raw materials; which may have a rule in modifying dosage form characteristics so that it became the main target for researchers to find new pharmaceutical excipients. Some of the plant extracts failed to give the desired characters while another extracts go further and became one of the official excipients in tablets, capsules as cellulose derivatives, pectin, shellac and polysaccharide-rich plant materials, which are successfully used as matrix formers in modified release dosage forms [1]. In addition, Phosphatidyle choline (natural extracts from soy bean) was used in preparation of nanoparticles as liposomes and transfersomes in transdermal drug delivery systems [2] Furthermore, plant extract could be modified chemically or physically to enhance their properties and get rid of some disadvantages as mold growth, and inter-source variation [3].

On the other hand plant components must be extracted and separated selectively in high degree of purity without un wanted materials, for that reason, many methods of extraction were developed according to the type of desired product and stability of the constituents [4]. Several solvent systems with different components and ratios were suggested for particular component extraction. The selection of particular solvent system is based on the selective solubility of the desired constituent in that solvent system. So that, each plant component should be extracted using unique extraction method, which must be developed a case by case [5]. The extract can be put back to dry from using a rotary evaporator or a freeze-drying [6].

Okra (*Abelmoschus esculentus L. (Moench*)) (fig. (1)) is widely distributed worldwide. It is cultivated for its green non-fibrous fruits or pods containing round seeds. The fruits are harvested when immature and eaten like a vegetable. Okra fruit and leaf considered as part of food menu in most countries especially in eastern Asia and middle east. Okra has many applications besides food making as: its roots and stems of okra are used for clarification of sugarcane juice, used in the paper industry [7]. Extract from okra seeds is an alternative source for edible oil. The greenish yellow edible oil has a pleasant taste and odor, and is high in unsaturated fats such as oleic acid and linoleic acid. The oil content of the seed is quite high at about 40%. Okra provides an important source of vitamins, calcium, potassium and other mineral matters which are often lacking in the diet in developing countries [8].

Fig. 1: Ripe Fruits of Okra

Pentoxifylline is a dimethylxanthine derivative indicated specifically in the treatment of intermittent claudication and other forms of chronic occlusive arterial diseases of the limbs [8.5]. PTX is completely absorbed after oral administration but it undergoes first-pass metabolism results in a low bioavailability "20%" and short half-life " 0.4-0.8 h", so that, PTX formulation in sustained release tablets could solve the problem of low oral bioavailability [9].

MATERIALS AND METHODS

Materials

Di-Sodium hydrogen phosphate was purchased from Reidele De-Haen AG, Seelze, Hannover, Germany. Acetone, Chloroform, CMC, Diethyl ether, Ethanol, Methanol, Sodium hydroxide and HCl, were purchased from BDH chemicals, Ltd., Liverpool, England. Pentoxifylline (PTX) was purchased from Slovakopharma, Slovenia, sodium di hydrogen phosphate and sodium chloride were purchased from E-Merk, Darmstadt, Germany. All another solvents and chemicals is within the analytical grade.

Methods

Okra extraction

Newly harvested ripped fruits of okra were collected from a local market in Al Najaf province in (in early of September 2013) and identified by taxonomist in Kufa University. Okra fruit was extracted using different solvent systems (as showed in Table (1)) in order to define the appropriate method of extraction. Okra extraction was performed for all extract with simple modification as required this method is summarized as follows: thoroughly rinse the fruits and cut it into small pieces using sharp knife then macerate it in particular solvent system in a closed vessel for appropriate time after that the extract was collected and dried using rotary evaporator. The dried extract was obtained and stored in well closed amber container [10]. The product finally was inspected for product ratio and mold growth to decide the successfulness of the extraction method. Variable solvent systems were tested to endeavor the optimum system and method of extraction [5].

Table 1: Okra extracts and different extraction procedure used

Name of the product	Solvent system used	Amount of okra (g)	Amount of solvent system (ml)	Time of maceration (days)	RPM used in Rotary evaporator	Temperature of drying using Rotary evaporator	Presence of seeds
OE_1	DW	200	QS to 800	5 days	25	32	Present
OE_2	10 % methanol	200	QS to 800	5 days	25	32	Present
OE_3	Acidified DW pH=3	200	QS to 800	5 days	25	32	Present
OE_4	Alkaline DW pH=9	200	QS to 800	5 Days	25	32	Removed
OE_5	DW	100	100	2days	25	50	Present
OE_6	20% methanol	100	130	2days	25	50	present
OE_7	DW: methanol 50:50 with HCl pH=3	3(kg)	5200	4 days	25	50	Removed
OE_8	DW: methanol 50:50 with NaOH pH=9	(3kg)	5000	4 days	25	50	Removed

QS means sufficient quantity

Table 2: Characterization of tablets prepared using okra extract as a binder

Name of the product	Mold growth	Presence of preservatives	Fate	Tablet formulation	Drug (PTX)	Disintegration	Friability	hardness	Dissolution
OE_1	+ ve	-ve	Discarded	-ve	Absent	-ve	-ve	-Ve	-ve
OE_2	+ ve	-ve	Discarded	-ve	Absent	-ve	-ve	-Ve	-ve
OE_3	- ve	-ve	Sustained	+ve	Present	+ve	+ve	+ve	- ve
OE_4	-ve	-ve	Sustained	+ve	Present	+ve	+ve	+ve	-ve
OE_5	-ve	-ve	Sustained	+ve	Present	+ve	+ve	+ve	-ve
OE_6	-ve	-ve	Sustained	+ve	Present	+ve	+ve	+ve	-ve
OE_7	-ve	+ve	Sustained	+ve	Present	+ve	+ve	+ve	+ve
OE_8	-ve	+ve	Sustained	+ve	Present	+ve	+ve	+ve	+ve

-ve: means not performed

Preparation of SR Okra extracts tablets

Wet granulation procedure

Okra extract other ingredients were comminuted and mixed in the mortar and pestle, then few drops of granulating laquir were added until a fluffy mixture was obtained (according to ball test). The resulted mass was passed through a mesh of one mm pore size to form large particles (granules) then dried at the atmospheric temperature.

Formulation of PTX SR tablets using Okra extracts as a binder

Okra extracts named (OE_3, OE_4, OE_5, OE_6, OE_7 and OE_8) was compressed to form tablets with PTX using the single punch and die tablet press and compression force (15 ton/inch^2).) as showed in Table [2]. In addition, multiple SR tablet formulas (F_{HCl} 1, F_{HCl} 2, F_{HCl} 3, F_{NaoH}1, F_{NaoH}2 and F_{NaoH}3) were prepared as above using 200 mg of PTX and 400 mg of okra extracts (OE_7 and OE_8) with varied amount of CMC as explained in table [3].

Characterization of prepared PTX SR tablets

Hardness test

Several tablets were prepared using okra extract was tested in terms of their hardness strength using the official Erweka hardness tester. Each tablet was put between jaws of the tester and runs it. The minimum force required to crush the tablet is recorded. This test was performed in triplicated manner [11].

Friability test

This measurement was carried out for all prepared formulas using Erweka friabilator. The loss in weight of tested tablets before and

after rotation should not exceed 1% of total weight of tablet [12]. Five tablets of each formula were weighed and revolved in friabilator drum at 25 RPM for 4 minutes, then the tablets were cleaned by fine brush and the total weight was recorded.

Table 3: Composition of PTX sustained release tablets prepared using okra extract

Formula Name	Type of okra extract	Amount of okra extract	PTX	CMC
F_{HCl} 1	OE_7	400mg	200mg	__
F_{HCl} 2	OE_7	400mg	200mg	50mg
F_{HCl} 3	OE_7	400mg	200mg	75mg
F_{NaoH}1	OE_8	400mg	200mg	__
F_{NaoH}2	OE_8	400mg	200mg	50 mg
F_{NaoH}3	OE_8	400mg	200mg	75mg

Disintegration test

A tablet was put into the jar of disintegration apparatus which is filled to the assigned level with distilled water. The temperature was adjusted at 37 °C and then the time required for complete disappearance of the tablet was recorded.

Dissolution test

Dissolution of PTX from prepared tablets was measured using Erweka dissolution apparatus USP basket method maintained at 37°C temp., and RPM = 50 [13]. Each jar was filled with 500 of simulated pH solution (Ph=2) for two hours then replaced with 500 ml of DW and perform the test as above for additional (9) hours. Samples of 5 ml were withdrawn at specific time intervals for 11 hours (and replaced with an equal amount of a fresh dissolution medium) using 0.2 micron Millipore filter and syringe, samples were filtered and measured spectrophotometrically at 273 nm. The test was done in a duplicated manner [14].

RESULTS AND DISCUSSION

Extraction of okra

According to data obtained, properties of okra fruit extract differ significantly according to the method used for extraction since simple maceration of comminuted okra fruit using in 1:4 okra: DW ratio (OE_1) failed to give an extract with acceptable properties as the amount produced is so small and the process is time consuming. In addition, OE_2 also gives the same results and this could be attributed to the large amount of menstrum used. Furthermore, OE 3 and 4 complain from the same problem of being hard to dry the extract due to the high amount of solvent.

In terms of mold growth, OE 1 and 2 were undergo fungi growth for all the product leading to discarding the extract, on the other hand, $OE_{3\ and 4}$ show a little of mold growth at the boundaries as shown in fig. (2).

Extraction of okra fruit using mixtures of DW and methanol with either HCl or NaoH and increased the temperature of drying gives more product in less time of maceration and drying. However, OE 7 and 8 were selected for preparation of PTX sustained release tablet due to their acceptable properties.

Presence of seed within okra fruit has great influence upon the properties of the final dried extracts since all the extracts($OE_{1,2,3,4,5\ and\ 6}$) contain the seed of okra, while upon removing of seeds the flexibility and gross properties of the dried extract get better and became gummy like rather than friable which represents a good property for and matrix former in tablet formulation. Using of preservatives (benzoic acid 0.1 %) sprayed over the dried extract is crucial in stabilization of the extract and prevents any mold growth (if any) [15].

Fig. 2: Mold growth on the surface of okra extract

Properties of prepared okra extract tablets

Eighty percent of extracts obtained during this experiment were granulated successfully and then compressed to form tablets. Prepared tablets in general, look shinny with no chips, cracks or any other tablet formulation faults as capping or lamination indication the excellent compressibility of okra extract as showed in fig. (3).

Furthermore, table (4) indicates a uniform weight of tablet without weight variation and uniform diameter of without variation and ranged between (10.09-10.12 mm) for OE_3 and OE_5 respectively.

Fortunately, strength of prepared tablets is acceptable since the lowest hardness is 76.6 N for OE_5, while OE_3 can with stand a compression force up to 150 N. This high hardness value is accompanied with low friability (maximum loss is about 0.21 % for OE_3 which is much lower than the maximum allowed percent (1%)[12]. This high tablet strength and low friability of prepared Tablet are correlated with the high value of tablet disintegration time (need more than 2hr); these properties make the okra extract a promising SR tablet former [16] as illustrated in table (4).

Effect of PTX addition

Extracts named $OE_{7\ and\ 8}$ were selected to prepare PTX sustained release tablets with CMC addition in different concentrations as showed in Table (3). Results obtained show that the addition of PTX has no significant ($p > 0.05$) effect on the diameter and on the friability properties of the tablets except for F_{NaoH} formulas which had greater friability (0.4 %) than the corresponding EO_8 but still within the acceptable range [17].

PTX addition increases disintegration time significantly ($p < 0.05$) for both extracts compared to plain tablets prepared as showed in both tables (4 and 5). On the other hand, tablet hardness increases significantly upon addition of PTX to $OE_{7\ and\ 8}$ but the increment is greater for F_{NaoH} 1 having hardness value about 163 N compared to 95 N for OE_8 having no PTX. In addition, significant decrease in

friability was recorded when PTX was added to both OE $_{7 \text{ and } 8}$ to be 0.03% and 0.097% for both F $_{Hcl}$ 1 and F_{NaoH} 1 respectively compared to plain tablets of OE $_{7 \text{and } 8}$ as shown on tables 8 and 9 indicating binding activity of PTX which has a significant Compressability [18].

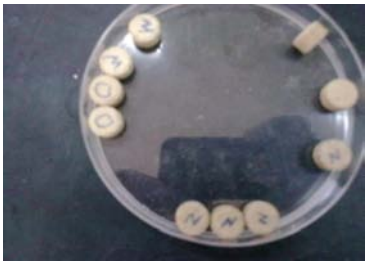

Fig. 3: Okra extract tablets

Effect of CMC Addition

Carboxy methyl cellulose was added in increasing concentration and its effects on SR tablets were recorded in Table (5). However, disintegration time increases with CMC concentration for both selected extracts and reaches 175 min for F_{NaoH} 3. In the same manner, tablet hardness increase significantely ($p< 0.05$) upon addition of CMC for both extracts, but the increament is much more significant in formulas prepared using OE_7 (214 N for formula contain 75 mg of CMC. Regarding tablet surface friability, addition of CMC leads to more friable tablets as F_{NaoH} 3 losses 0.4 % of its weight compared to tablets obtained from OE_8 which losses only 0.07 % of its weight as showed in Table (5). These results are agreed with the binding activity of CMC and results obtained by Cantoni et al [19] and disagree with findings of Anoop Kumar and co workers [20].

Dissolution profiles of PTX from Okra extracts tablets

The major factor determines the successfulness of any SR polymer is the ability to retard the release of water soluble drug for more than 10 hours. All tablets prepared using the selected extracts (OE $_{7 \text{ and } 8)}$ were analyzed for the rate of PTX release from their matrices. Results obtained shows a typical SR release zero order of PTX from the matrix for both extracts.

CMC has no significant influence in PTX release from formulas F_{Hcl} 1,2 and 3 since PTX release about 80 % in 6 hours with no significant effect for CMC as showed in fig. (4). On the other hand, CMC extends the release of PTX to be more uniform and reproducible and following zero order kinetic about (10 mg per hour) for 10 hours as shown in fig. (5) and these results make okra extracts a promising SR release binder capable for retardation of water soluble drugs as PTX in presence of channeling agent as CMC.

Table 4: Properties of tablets prepared using different okra extracts

Name of the product	Solvent system used	Mold growth	Fate	Average weight (g) (n=10)	Average thickness (mm	Average diameter (mm)	Average Disintegration time	Average hardness (N) (n=3)	Percent lost after friability test (n= 3)
OE_1	DW	+ ve	Discarded						
OE_2	10 % methanol	+ ve	Discarded						
OE_3	Acidified DW pH=3.5	- ve	Sustains	0.5825	6.15 mm	10.063 mm		150 N	0.21 %
OE_4	Alkaline DW pH=9	-ve	Sustained	0.596	6 mm	10.07 mm		95 N	0.17 %
OE_5	DW	-ve		0.5875	6.14 mm	10.12 mm		76.6 N	
OE_6	20% methanol	-ve		0.58	6.19 mm	10.096 mm		82.3 N	
OE_7	DW: methanol 50:50 with HCl pH=3	-ve		0.5825	6.15 mm	10.063 mm		150 N	0.21 %
OE_8	DW: methanol 50:50 with NaOH pH=9	-ve		0.596	6 mm	10.07		95 N	0.17 %

Table 5: Properties of PTX sustained release tablets prepared using selected okra extracts

Formula Name	Type of okra extract	Average weight (n=10)	Average thickness (mm)	Average diameter (mm)	Average Disintegration time (min)	Average hardness (N)	Percent lost after friability test
F_{HCl} 1	OE_7	0.59 g	6 mm	10.03 mm	100 min	172 N	0.03 %
F_{HCl} 2	OE_7	0.63 g	6.5 mm	10.03 mm	120 min	200 N	0.18 %
F_{HCl} 3	OE_7	0.68 g	6.79 mm	10.04 mm	150 min	214 N	0.15 %
F_{NaoH}1	OE_8	0.585 g	6.2 mm	10.1 mm	99 min	163 N	0.097 %
F_{NaoH}2	OE_8	0.64 g	6.92 mm	10.13 mm	135 min	181 N	0.121 %
F_{NaoH}3	OE_8	0.66 g	7.122 mm	10.11 mm	175 min	193 N	0.4 %

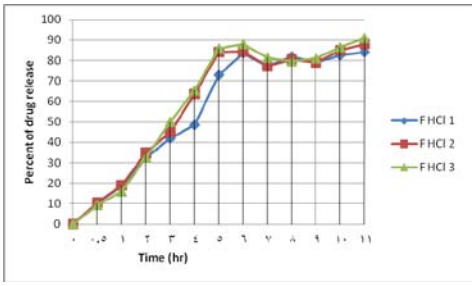

Fig. 4: Release profile of PTX from SR tablet prepared using okra extract OE_7

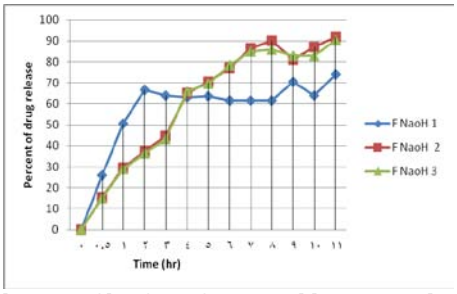

Fig. 5: Release profile of PTX from SR tablet prepared using okra extract OE_8

CONCLUSION

okra mucilage could be extracted using many solvent system and the properties of okra extract is greatly affected by solvent constituent and pH of the solvent. Okra extract succeeded to produce tablets with acceptable properties and could retard the release of water soluble drug as pentoxifylline to decrease dosing frequency using novel retarding agent obtained from cheap available source. Okra extract succeeded in a formation of the sustained release tablet with acceptable retardation value. Addition of CMC extends the disintegration time and leads PTX release to be uniform and follow zero order kinetics.

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CONFLICT OF INTERESTS

Declared None.

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