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Research Article

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Development and evaluation of sustained release matrix tablets of ketoprofen employing natural polymers (pomegranate peel and acacia powders)

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ABSTRACT

In the present study, we developed sustained release matrix tablets of ketoprofen using natural polymers (pomegranate peel and acacia powders) in different formulations. The tablets prepared by wet granulation method were subjected to evaluation for pre-compression parameters including: bulk density, tapped density, compressibility(Carr's index) and Hauser's ratio. Also, the prepared tablets were subjected to evaluation for post - compression parameters including: weight variation, drug content, hardness and friability tests. All physical characters of fabricated tablets were within the acceptable limits of pharmacopoeia. In vitro release studies showed that different formulations exhibited sustained release of ketoprofen over ten hours period. It was concluded that the used polymers (pomegranate peel and acacia powders) can be used as sustained release matrix tablet to provide sustained release of ketoprofenin order to extend the duration of its action, reduce the frequency of dosing and increase patient compliance.

Keywords: ketoprofen, polymers, pomegranate peel powders, acacia powders, sustained release matrix tablets.

INTRODUCTION

The plant based polymers have been studied for their application in different pharmaceutical dosage forms like matrix controlled system, film coating agents, buccal films, microspheres, nanoparticles, viscous liquid formulations like ophthalmic solutions, suspensions, implants and their applicability and efficacy has been proven. These have also been utilized as viscosity enhancers, stabilizers, disintegrants, solubilizes, emulsifiers, suspending agents, gelling agents, bioadhesives and binders in different dosage forms(1,2). A polymeris a large molecule (macromolecule)composed of repeating structural units. These subunits are typically connected by covalent chemical bonds. Both synthetic and natural polymers are available but the use of natural polymers for pharmaceutical applications has been attractive because they are economical, readily available and non-toxic. They are capable of chemical modifications, potentially biodegradable and with few exceptions, also biocompatible (3).

The pomegranate peel powder is a natural powder obtained from Punicagranatum, family Punicaceae, which is a small tree originating from Asia and cultivated throughout the Mediterranean region, China, India, South Africa, and the Americas. Pomegranate peel, since ancient times, has been used to treat several diseases. In recent times, the plant has attracted the interest of researchers in examining its composition and biological properties. The fruit is consumed mainly fresh or in beverage, and is a rich source of phenolic compounds, including hydrolyzable tannins, which possess high antioxidant activity, ellagitannins are the major polyphenols found in pomegranate fruit (4-6). Punicalagin, the main ellagitannins in pomegranate, has low cytotoxicity in vitro and is not toxic to rats when administered orally, A pomegranate ellagitannins-enriched dietary supplement proved to be safe for human after 28 days of treatment, and no changes have been reported in hematological, biochemical, or urinary analysis (7-9). Arabic gum is the dried sticky exudation acquired from the stem and branches of Acacia Arabica obtained from Valerie's Solanaceae, belonging to family Leguminosae. The gum has been recognized as an acidic polysaccharide

holding D-galactose, L-arabinose, L-rhamnose, and D-glucuronic acid, Acacia may be principally utilized within oral and topical pharmaceutical formulations as a suspending and emulsifying agent, often in mixtures with Tragacanth. It is utilized in the preparation of pastilles, lozenges and as a tablet binder (10).Gum Arabic might have been effectively utilized as a matrix microencapsulating agent for the enzyme, endoglucanase, which proofed to provide a slow release of the encapsulated enzyme and in addition increased its stability (11).

ketoprofenis a non-steroidal anti-inflammatory drug with analgesic and antipyretic properties. In anti- inflammatory models, ketoprofen has been shown to have inhibitory effects on prostaglandin and leukotriene synthesis, to have antibradykinin activity, as well as to have lysosomal membrane-stabilizing action, However, it's mode of action like that of other NSAIDs, is not fully understood. ketoprofen also used in the treatment of rheumatoid arthritis, osteoarthritis, primary dysmenorrhea and acute pain (12). In this work, sustained release matrix tablets were fabricated from pomegranate peel and acacia powders. The formed tablets were characterized and evaluated for prolonged delivery of ketoproen.

EXPERIMENTAL SECTION

Materials

Pomegranate peel powders were purchased from local suppliers and all other chemicals were kindly provided by Modern Pharma, Sana'a, Yemen and were of analytical grade.

Methods

Preparation of sustained release matrix tablet

Twelve different formulations of ketoprofen matrix tablets with natural polymers pomegranate peel and acacia powders according to table (1) were prepared by wet granulation methods. Ketoprofen, natural polymers diluents, binders, lubricant and glidants were weighed and passed through sieve no.30-mesh(13).Then ketoprofen, polymers, diluents and binders were mixed, then a sufficient volume of granulating agent (isopropyl alcohol) was added slowly to form enough cohesiveness mass in stainless steel container by rotating the wet mass by stainless stile rod. The wet mass formed was sieved through sieve no. 16-messh to obtain wet granules. The formed wet granules were dried at 40c for 30 minutes, Thereafter, the dried granules were passed through sieve no. 16-mesh to resize the granules. Then Talc and magnesium stearate as glidants and lubricant for each formulation were added and mixed thoroughly. The powder was transported into the tablets machine, finally the mixture of tablet granules were a compressed in 8.2mm diameter standard concave punches using rotary compression machine (Erweka, Germany)(14).

Table (1):Formulations of ketoprofen matrix tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
ktoprofen	100	100	100	100	100	100	100	100	100	100	100	100
Pomegranate	30	50	70				30	50	70	30	50	70
Acacia				30	50	70						
Microcrystallin cellulose	54	34	14	54	34	14						
Polyvinyl pyrolidine	10	10	10	10	10	10	10	10	10			
Dicalcium phosphate							54	34	14	54	34	14
Isopropyl alchol	4ml	4ml	4ml	4ml	4ml	4ml	4ml	4ml	4ml	4ml	4ml	4ml
Magnesim stearate	4	4	4	4	4	4	4	4	4	10	10	10
Talc	2	2	2	2	2	2	2	2	2	6	6	6
Total	200	200	200	200	200	200	200	200	200	200	200	200

Characteristics and evaluation of granules

Bulk density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. Twenty grams of granules from each formula, previously shaken to break any agglomerates formed, was introduced in to 100 ml graduated measuring cylinder of digital automatic tap density tester (TAP II, Veego, India) and the volume of granules was measured and V_0 noted. After that Tapping was started until no further change in volume was noted (15). LBD and TBD were calculated using the following equations. LBD= Weight of the granules /Untapped Volume of the packing, TBD = Weight of the granules /Tapped Volume of the packing.

Compressibility index

The Compressibility Index of the granules was determined by Carr's (compressibility) index. It is a simple test to evaluate the LBD and TBD of a granules and the rate at which it packed down (16). The formula for Carr's Index is: Carr's index (%) = [TBD-LBD] X 100 /TBD].

If the value of compressibility index or Carr's index is equal to 5-15% it indicates excellent flowability of granules. If the value is equal to 12-16%, it indicates good flowability. If the value of compressibility index (Carr's index) is equal to 18-21%, it indicates fair flowability. Finally, if the value of compressibility index (Carr's index) is greater than 25%, it indicates that the flowability of granules is poor.

Hausner Ratio

Hausner ratio is used to determine the flowability of powders which are used in pharmaceutical preparation.
Hausner ratio, is determined according to the equation:

$$\text{Hausner ratio} = \frac{\text{Tapped density (TD)g/ml}}{\text{Bulk density (BD) g/ml}}$$(17).

If the value of Hausner ratio is less than (<1.25) it indicate a powders that is freely flowability, whereas, if the value of Hausner ratio is a greater than 1.25 (>1.25), it indicates that the powder is poor flowability,

Evaluation of tablets

Weight variation test

To study weight variation, twenty tablets were selected randomly from each formulations F1-F12 and weighed individually to check for weight variation(18).

Drug content

Five tablets were weighed individually and powdered. The powder equivalent to average weight of tablets was weighed and drug was extracted in phosphate buffer pH 7.4.The drug content was determined using waters HPLC and measuring the absorbance at λ max = 260 nm(19).

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined by using Erweka-type, Germany hardness tester. It was expressed in kg/cm^2.five tablets were randomly picked and hardness of the tablets was determined (15).

Friability test

The friability of tablets was determined using Veego Friabilator(VFT-India). Twenty tablets were initially weighed and transferred into Friabilator. The Friabilator was operated at 25rpm for 4 minutes. The tablets were weighed again. The % friability was then calculated by formula %F =1-(loss in weight/ initial weight)100%. Friability of tablets less than 1% are considered acceptable(20).

In Vitro release

The in vitro release of ketoprofen from the formulated tablets was carried out in tablet dissolution tester DT6R, Erweka, Germany. USP paddle method was selected to perform the release study of ketoprofen using 900 ml of dissolution medium of phosphate buffer (pH7.4) maintained at 37.0 ±0.5°C and a stirring rate of 100 rpm. Six tablets from each formulation were tested individually in phosphate buffer (pH7.4) for the following 10 h. At every 15 minutes interval for the first hour of dissolution and 45 minutes until complete the dissolution process, samples of 5 ml were withdrawn from the dissolution medium and replaced with fresh medium to maintain the volume constant. After filtration and appropriate dilution, the amount of drug substance present in each sample was determined spectrophotometrically at lambda max (λ max =260 nm (21).

RESULTS AND DISCUSSION

Initially tablets were prepared with drug to polymer (pomegranate peel and acacia powders) in ratio 1:0.30, 1:0.50 and 1:0.70 in all formulations which were represented in table (1).The granules of various formulations were prepared and evaluated for bulk density, tapped density, compressibility(carr'sindex) and Hausner ratio, table(2).All the values were within an acceptable limit.

Table (2): Pre-compression parameters of ketoprofengranules

Formulation code	Bulk Density (gm/ ml)	Tapped Density(gm/ml)	Compressibility(carr's index %)	Hausner Ratio(gm/ ml)
F1	0.141	0.172	18.023	1.22
F2	0.045	0.053	18.87	1.18
F3	0.045	0.051	15.69	1.133
F4	0.050	0.057	12.28	1.14
F5	0.045	0.055	18.18	1.22
F6	0.045	0.053	15.09	1.18
F7	0.051	0,063	19.05	1.24
F8	0.050	0.060	16.66	1.2
F9	0.051	0.064	20.31	1.3
F10	0.057	0.059	12.38	1.035
F11	0.054	0.055	13.18	1.02
F12	0.052	0.063	17.46	1.212

The tablets of various formulations were evaluated for hardness, friability, drug content and uniformity of weight and results are represented in table (3).

Table (3): Post-compression parameters of ketoprofen matrix tablets

Formulation code	Average weight ±SD (n= 20)	Hardness ±SD(n=5)	Friability %(n=20)	Drug content %(n=5)
F1	204.9 ± 4.2	9.56 ±0.67	0.31	102.27 ± 0.06
F2	205.89 ± 3	10.68±0.84	0.72	102.13± 0.06
F3	204.99 ± 3.4	11.2±0.37	0.33	103.27 ± 0.06
F4	207.49 ± 1	9.58±0.37	0.14	106.47 ± 0.06
F5	207.39 ± 1.2	9.9±0.51	0.21	106.47 ± 0.06
F6	207.49 ± 1.3	9.92±0.67	0.31	106.57 ± 0.06
F7	200.59 ± 2.5	10.8±0.40	0.32	102.87 ± 0.06
F8	201.89 ± 3	11.5±0.24	0.27	105.47 ± 0.06
F9	201.89 ± 1.6	11.74±0.61	0.24	104.77 ± 0.06
F10	202.39 ± 2	8.74±0.63	0.81	100.63 ± 0.06
F11	202.49 ± 0.9	10.74±0.22	0.50	101.53 ± 0.06
F12	202.39 ± 1.9	11.52±0.22	0.70	103.77 ± 0.06

The weight variation tests were performed according to the procedure given in the pharmacopoeia. In a weight variation test, pharmacopeial limit of tablet for percentage deviation is 7.5%. The average percentage deviation of all tablet formulation was found to be within the pharmacopeial limit and hence all formulations passed the test for uniformity of weight.

The friability of all formulation was below the 1% limit shown in the pharmacopoeia indicating that the friability is within the standard limit. The drug content of all formulation was in between 100.63% - 106.47% ±0.06%. All values of formulation was found to be within the pharmacopeial limits. Figures 1-4 show the in vitro release of ketoprofen formulation 1-12. The represented data demonstrate the ability of these delivery system to prolong the release of ketoprofen for up to 10 hours in all formulations. All formulations showed satisfactory sustained release capability with minor variations in releases profile. Using higher concentrations of the polymer led to a decrease in release rate, From previous studies, which are similar to our study: G.N.K. Ganesh et al, 2010(22).

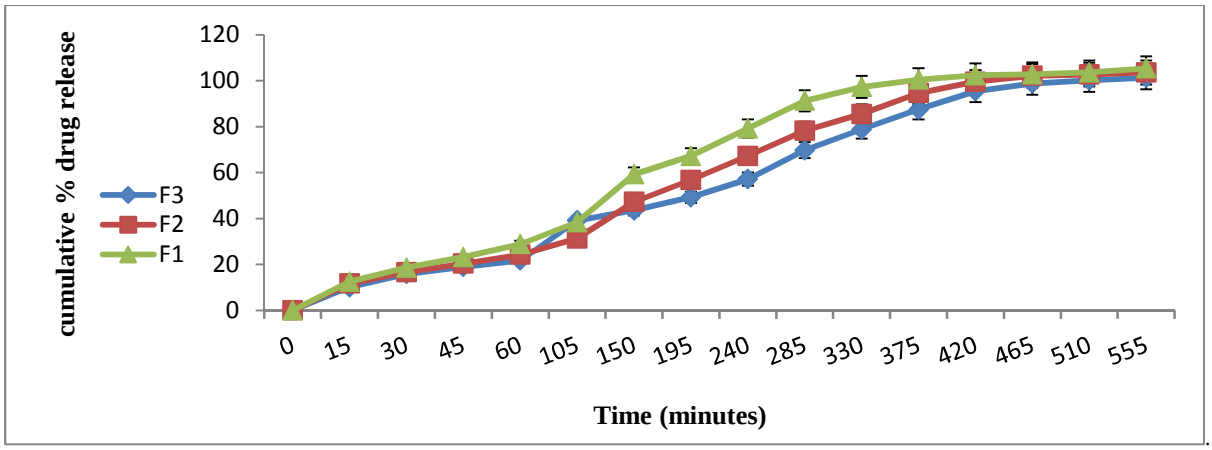

Figure (1): In vitro drug release behaviors of formulation of ketoprofen with natural polymers (pomegranate peel powder) F1-F3 (n=6)

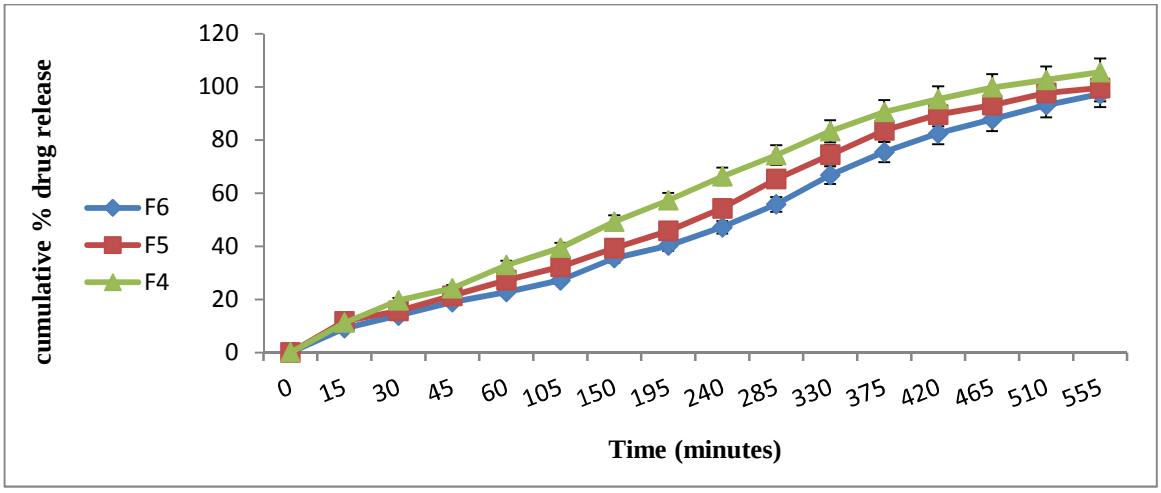

Figure (2): In vitro drug release behaviors of formulation of ketoprofen with natural polymers (Acacia powder) F4-F6 (n=6)

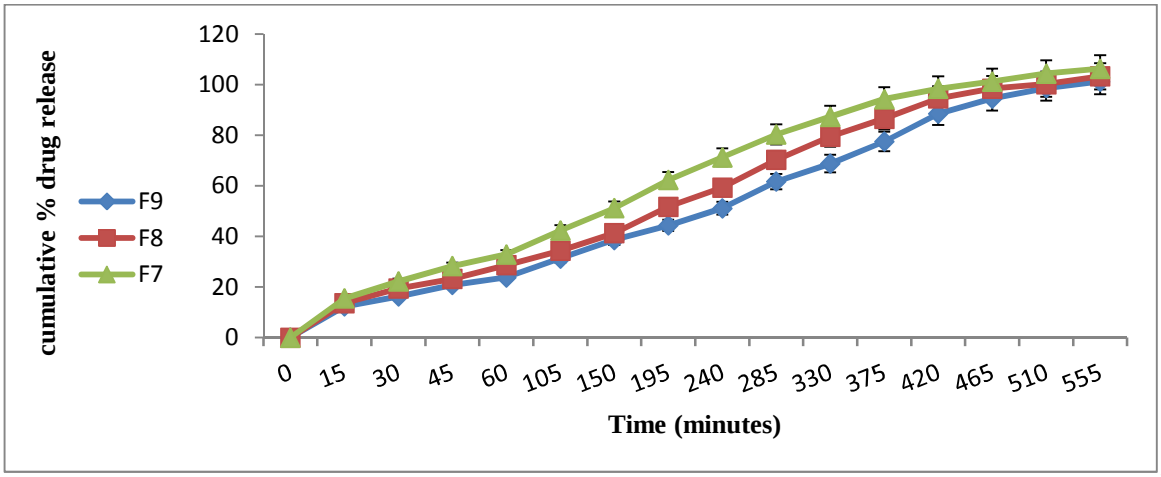

Figure (3): In vitro drug release behaviors of formulation of ketoprofen with natural polymers (pomegranate peel powder) F7-F9 (n=6)

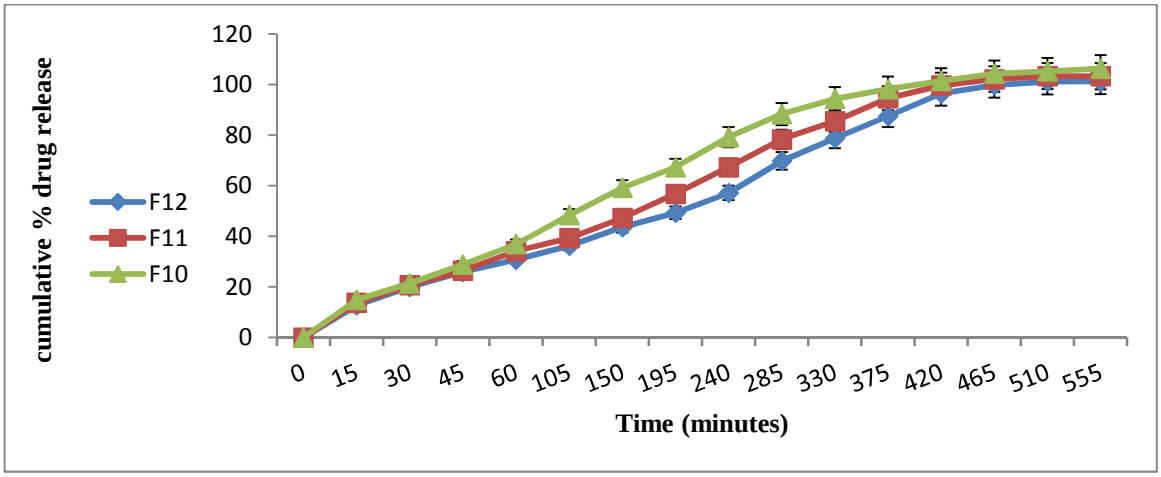

Figure (4): In vitro drug release behaviors of formulation of ketoprofen with natural polymers (pomegranate peel powder) F10-F12 (n=6)

CONCLUSION

This study showed the feasibility of developing oral sustained release formulation through matrix tablets employing natural polymers including pomegranate peel and Acacia powders. Our results show that the formulated matrix

tablets of ketoprofen using natural polymers pomegranate peel and acacia powders were capable of exhibiting sustained release properties. This will consequently lead to reducing the dose intake, minimizing the blood level oscillations, reducing dose related adverse effect and cost and ultimately improve the patient compliance.

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