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Preparation and In-vitro Evaluation a modified release dosage forms of paracetamol using propolis supplement powder as matrix forming agent

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Abstract:

The Purpose of present study was to prepare and evaluate new modified release formulations of paracetamol using supplement powder of propolis (bee glue) as matrices for release. Two types of formulations were prepared (physical blends of drug and propolis powder and solid matrix form by solvent evaporation method). Pre compression (compressibility index, hausner ratio and angle of repose) and post compression (hardness, friability and disintegration tests) evaluation studies were done. Tablets and capsules were prepared for paracetamol formulations. The drug: propolis powder interaction was evaluated by FT-IR spectroscopic method**.** The dissolution rate of the formulations was studied by USP dissolution. The data of release were subjected to different models in order to determined their release mechanisms and kinetics. The results show that, the drug release (87 %, 85.9% and 73% which is in the order of F1>F2>F3 at 5 hrs) was higher from the formulation prepared by direct compression of physical blends as compared to solid matrix formulations prepared by solvent evaporation method(42.5 %, 40.8 % and 33.6 % for FM1, FM2 and FM3 respectively)**.** Drug release kinetics shows the drug release by nonfickian diffusion mechanism**.** Results indicate that incorporation of propolis powder in the formulations decreased drug release and the tablet formulation was better in comparison with capsules formulation. The developed propolis matrix tablets of parcetamol may be used for modified release of drug.

Keywords: paracetamol, propolis powder, modified release.

تحضير وتقييم مختبري لشكل دوائي معدل التحرر لعقار البارستومول بأستخدام مسحوق العكبر كقالب تشكيل

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الخلاصة:

الغرض من الدراسة الحالية هو لتحضير وتقييم صيغ جديدة معدلة التحرر للعقار البراستامول باستخدام باودر البروبولس كقالب تحرر.نوعين من الصيغ تم تحضيرها (الخليط فيزيائي من العقار وباودر البروبولس و صيغة القالب الصلب بواسطة طريقة تبخير المذيب). تم عمل دراسات تقييم الى ما قبل الكبس (زاوية ألاستناد نسبة هاوسنر ومؤشر قابلية الانضغاط) وما بعد الكبس(اختبارات الصلابة والتفتت والانحلال). وقد تم تحضير اقراص وكبسولات لصيغ البراستامول. تفاعل العقار مع باودر البروبولس تم تقييمه بواسطة مطياف الاشعة تحت الحمراء. ان معدل الذوبان للصيغ

تم دراستها حسب ذوبانية الدستور الامريكي. كما ان بيانات التحرر خضعت لموديلات مختلفة لغرض تعيين الية وحركية التحرر. النتائج اظهرت ان تحرر العقار (*85.9% ,87 %، 73% عند الساعة خمسة F1>F2>F3*) كان اعلى من الصيغ المحضرة بواسطة الكبس المباشر للخليط الفيزيائي بالمقارنة بصيغ القالب الصلب المحضرة بطريقة تبخير المذيب(42.5%، 40.8%، 33.6% لFM1, FM3, FM2بالتوالي). ان حركية تحرر العقار اظهرت ان تحرر الدواء بالية نفوذية النونفيكين. النتائج اظهرت بان دمج باودر البروبولس بالصيغ يقلل من تحرر الدواء وان صيغة القرص افضل بالمقارنة بالكبسولة. ان تطوير اقراص البروبولس الصلبة للعقار البراستامول يمكن ان تستخدم لتعديل تحرر الدواء.

Introduction:

Oral route is considered most accepted, suitable and not dangerous owing to its simplicity of administration, patient acceptance, and successful developed process. It is the mainly broadly employed way of drug administration along with all the other ways. Pharmaceutical products intended for oral delivery are mostly immediate release type or usual drug delivery systems, which are designed for rapid release of drug and absorption [(1)]. Modified release dosage forms are drug delivery systems which provide the release of drug in a modified way, which, by asset of formulation and product design, provide drug release in a modified form different from that of the conventional dosage forms. The most important benefits of modified release dosage forms are to [(2)]:

- reduce problems with patient compliance
- reduce the variation of drug blood level
- reduce dosing frequency
- reduce local or systemic side effects
- reduce overall healthcare costs

Modified release dosage forms are either single –unit dosage forms (include tablets, coated tablets, matrix tablets and some capsules) or multiple-unit dosage forms (includes granules, beads, capsules and microcapsules) [(3)]. There are many categories of modified release dosage forms for examples, diffusion systems, dissolution systems, osmotic systems, Ion-exchange resins, mucoadhesive systems and floating systems[(4)].

Reservoir device and matrix device are the two types of diffusion systems. In a reservoir device, the core of the drug is enclosed by a polymeric membrane, which determines the rate of drug release based on Fick's first law. In a matrix device, the drug is mixed homogenously with the polymer matrix such as bees wax and carnauba wax[(5)]. However, the simple approaches to produce of modified release dosage forms involves the direct compression of blends of drug, modifier materials and additives to form a tablet in which drug is embedded in modifier matrix. On other hand, blends of modifier and drug may be granulated before compression. The physicochemical properties of the drug, the type of the product to be obtained and the purpose of the dosage form. All these factors propose the type of polymer that will be used. Abroad range of polymers can be used to form matrix system, which consist mostly of natural or artificial macromolecular polymer such as Hydrophobic Matrices (include polyethylene, polyvinyl chloride, ethyl cellulose and acrylate polymers and their copolymers), lipid Matrices (Carnauba wax in combination with stearyl alcohol or stearic acid) and Hydrophilic Matrices(Cellulose derivatives and Non cellulose natural or semi synthetic polymers for example Alginates, chitosan and modified starches)[(4)].

Propolis is a natural resinous substance collected by bee from plant secretions. Bees employ it chiefly to coat the hive interior and the breeding cells and to mend fissure and crevices. Propolis is composed of 50% resins, 30% waxes and fatty acids, 10% essential oils, 5% pollens and 10% minerals and other organic compounds[(6)].

Propolis has important pharmacological properties and it can be used for a wide range of reasons such as, anti-inflammatory, antioxidant and antitumor activity, antibacterial, antifungal,

antiprotozoan, antiviral, and immunomodulatory[7]. propolis has a strong hepatoprotective effect against acute hepatic damage and subchronic hepatic injury induced by CCl4[8] and acetaminophen[9]. Recently, alcoholic and chloroform extract of propolis was used in preparation of controlled release dosage form of indomethacin[10].

Paracetamol is widely used as analgesic and antipyretic medicine and, however it is safe when used at therapeutic doses. paracetamol is mainly metabolized in the liver by glucuronidation and sulfation. Paracetomol is a powerful inducer of cytochrome P450 and little amount drug is metabolized by the cytochrome P450 into the reactive intermediate Nacetyl- p-benzoquinoneimine (NAPQI), which is usually detoxified by glutathione (GSH). GSH is exhausted by NAPQI when overdose is used. Overload of NAPQI causes oxidative stress and binds covalently to liver proteins [11]. In general the metabolizing enzymes in liver detoxify many xenobiotics and bioactivate the toxicity of others, so that liver is the first organ exposed to the harmful effects of toxic material. Paracetamol overdose in both animals and man has been shown to produce hepatic necrosis. For that reason, protective agent for liver are of particular interest[12].The objective of this study was to prepare and evaluate a modified release solid dosage form for paracetamol using supplement powder of propolis as matrices. In same time the addition of propolis in paraceamol preparation may be reduce the liver toxicity of paracetamol since it act as hepatoprotective agent.

Methods and Materials:

Materials

Paracetamol was obtained as gift from Al-Safa pharmaceutical industries Company-Iraq. Propolis powder supplement was purchased from Y.S organic bee farm (USA).Potassium dihydrogen phosphate -BDH chemical Ltd-Pool, England. Starch maize-May and Baker-Dagenham England. Other materials and solvents used were of analytical grade.

Pre compression evaluation for physical mixing

The powder blend of drug, propolis powder and lactose was prepared using different ratio of drug and propolis as shown in table 1 and it was evaluated for flow properties and compressibility as follows[13].

Bulk Density (Bd)

Bulk density (Bd) was determined by transferring the blend into a graduated cylinder. The bulk volume (V_B) and weight of the powder (M) was determined. The bulk density was calculated using the following formula.

$Bd = M/V$

Tapped Density (Td)

A well-known mass of blend was tapped in a graduated cylinder for a predetermined time. The weight (M) and volume of the blend in the cylinder (V_T) was measured. The tapped density (Td) was calculated using the following formula,

$Td= M/ V_T$

Angle of Repose

Powder blends were allowed to flow freely through a funnel onto the center of an upturned petridish until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and the angle of repose (q) was calculated using the following equation.

$Tan\ q=(h/r)$

Compressibility Index

Carr's index or compressibility index is the indirect measure of various powder characteristics. It is the straightforward method for determination of followability, in which the compressibility index (carr's index) can be calculated as follows:

$I= V_B-V_T/V_T$ Where, V_B is the bulk volume and V_T is tapped volume.

Hausner ratio

Hausner ratio11 is an indirect index of simplicity of powder flow. Hausner ratio

(Hr): This was calculated from Td and Bd using the following expression [14].

IH = Td/Bd.

Matrix preparation

Solvent evaporation method was used in preparation of matrix. Different formulas were prepared by this method as mention in table 1 .A matrix of propolis that contain drug particles can be formed by dispersing drug and propolis powder in ethanol 96% for one hour, after that the solvent was allowed to evaporate.

Dosage form preparation

Direct compression method was used to form tablet. On other hand, powder blend was granulated before compression for matrix form. In addition to that capsule dosage form was also formed for matrix form

Evaluation of dosage form

Tablets were evaluated for different parameters as hardness, thickness, diameter, friability, disintegration and in vitro dissolution study. Capsule form was evaluated for dissolution only.

Hardness

The hardness, thickness and diameter of tablets were determined using the Erweka hardness tester (GmbH, Germany) [15].

Friability test

Twenty tablets were weight and placed in the Erweka friabilator(GmbH, Germany). The friability is specified by the following formula:F=(1-W/Wt)x100

Where, W is the weight of the tablets before the test and W_t is the weight of the tablet after the test [15]

Disintegration test

The disintegration time was determined in distil water using disintegration apparatus(Erweka, GmbH, Germany) . Six tablets were placed in each tube of the basket and the time for complete disintegration of each tablet was recorded [16].

Table 1: Composition of Different Dosage Forms of Paracetamol

Formula code	Drug mg	Propolis mg	Lactose mg	Starch mg
Physical blends for tablet dosage form				
F1	150	75	275	-
F2	150	150	200	-
F3	150	300	50	
F4	150	-	200	150
Matrix form for tablet dosage form				
FM1	150	75	275	-
FM2	150	150	200	-
FM3	150	300	50	-
Matrix forms for capsule dosage form				
FMC1	100	50	350	-
FMC2	100	100	300	-
FMC3	100	200	200	-
FMC4	100	300	100	-
FMC5	100	400	-	
FC6	100	-	400	

Fourier transform, infrared (FTIR) study

The pure drug paracetamol, propolis supplement powder, and a mixture of drug with propolis powder were mixed separately with infrared (IR) grade KBr and corresponding pellets were prepared by applying a pressure. The pellets were scanned in an inert atmosphere over a wave number range of 4000–400 cm^{-1}FTIR instrument (IR Affinity- 1-Shimadzu, Japan) [17].

In vitro drug release

In vitro drug release of paracetamol from formed dosage forms(tablet, capsule and free beads) was determined using USP dissolution testing apparatus II (Paddle type) (Erweka, GmbH, Germany).The dissolution test was performed using 900 ml of phosphate buffer (pH 6.8) at 37 ± 0.50C. The speed of rotation of paddle was set at 50 rpm. At a suitable time interval; 5 ml samples were withdrawn. Concentration of drug in each sample was calculated by using UV spectrophotometer at 243 nm [18].

Results and discussion:

Pre compression studies

Blend of drug and propolis was prepared and evaluated for flowing properties for F1.F2, F3and FM1 formulas as shown in table 2. Bulk density was found between 0.476 and 0.526 gm/cm^3 and the blends showed tapped density of 0.625 gm/cm^3 for F1, F2 and F3 Formulations. From density data compressibility index and hausner ratio were calculated and were found between 15.84% 23.84 and between 1.188 and 1.31respectively. . Angle of repose was also calculated and was found in the range of 33.6˚ and 43.02˚. The results indicate that as the concentration of propolis powder was increased, the flowability of blend was improved and candidate for direct compression. Results were also indicated that FM1shows fair to poor flowabilty.

Table 2: Evaluation of Mixed Blend of Drug and Propolis Powder

Formula code	Bulk density g/cm^3	Tapped density g/cm^3	Angle of repose ^{o}	Compressibility index %	Hausner ratio
F1	**0.476**	**0.625**	**43.02**	**23.84**	**1.188**
F2	**0.5**	**0.625**	**37.5**	**20**	**1.25**
F3	**0.526**	**0.625**	**33.6**	**15.84**	**1.31**
FM1	**0.566**	**0.85**	**39.8**	**33.41**	**1.5**

Post compression studies

The data of results show that the hardness of tablets prepared by direct compression of physical blends was found to be in the range of 55.5 to 93.5 N , while the hardness of solid matrix tablets was found between 94 and 168 N as given in tables 3 this, reflects the rigidity and rearrangements of powder particles . Friability of the tablets were found below 1 % for formulas F3, FM1, FM2 and FM3 indicating a good mechanical resistance of tablets. In addition to that, the disintegration time was found to be more than two hours for FM2 and FM3 formulations this may be to the effect of propolis components (waxy material) on disintegration of tablet and form a coat on drug particles.

Table 3: Evaluation of Tablet Forms.

Formula code	Hardness ± SD (Newton)	Diameter ± SD (mm)	Thickness ± SD (mm)	Friability % lose	Disintegration ± SD (min)
F1	**55.5±1.11**	**10.067±0.004**	**5.43±0.023**	**% 8.090**	**12.376±0.254**
F2	**53.5±2.061**	**10.055±0.011**	**5.325±0.018**	**%2.600**	**12.51167±0.32**
F3	**93.5±5.22**	**10.07±0.01**	**5.425±0.018**	**%0.801**	**33.873±3.701**
F4	**83.75±0.43**	**10.037±0.01**	**5.262±0.029**	**%2.390**	**0.956±0.03**
FM1	**94±0.7071**	**10.285±0.355**	**5±0.018708**	**%0.620**	**26.25±6.1**
FM2	**153.25±24.0**	**10.037±0.016**	**4.995±0.018**	**%0.891**	**>120**
FM3	**168±1.5811**	**9.995±0.022**	**5.11±0.0458**	**%0.631**	**>120**

Compatibility study

Figure 1 and 2 show the IR spectrum of paracetamol and propolis powder supplement respectively, while figure 3 show the physical mixture of drug with propolis powder. The spectrum in mixture of drug and propolis is similar to that of paracetamol alone. The usual occurrence of 1371.39 cm^{-1} and 1440,83 cm^{-1} for O-H in plane bending and-----C stretching respectively of paracetamol were present in their positions. The N-H bending of secondary amide was appeared at normal frequency 1610.cm^{-1} as well as the C=O of secondary amide was appeared at 1654cm^{-1} .O-H stretching of phenolic OH and The N-H stretching of secondary amide were also occurred at 3163 cm^{-1} and 3327 cm^{-1} ,respectively. There is no appearance of new bands for new functional group or disappearance of important bands. In general, no predominant drug interaction was detected.

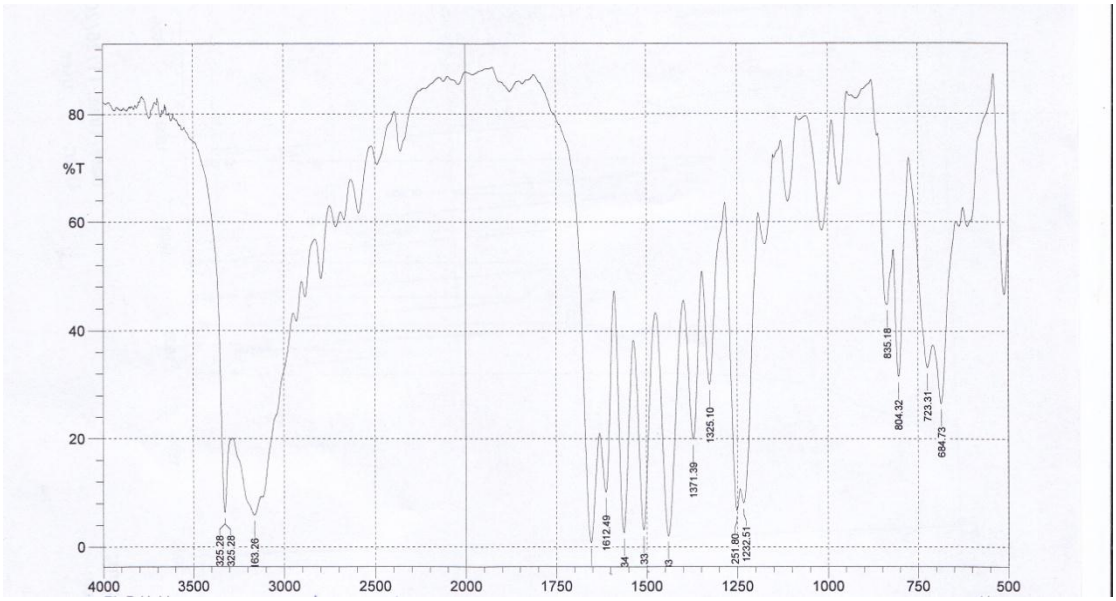

Figure 1: Fourier Transform Infra Red (FTIR) of paracetamol.

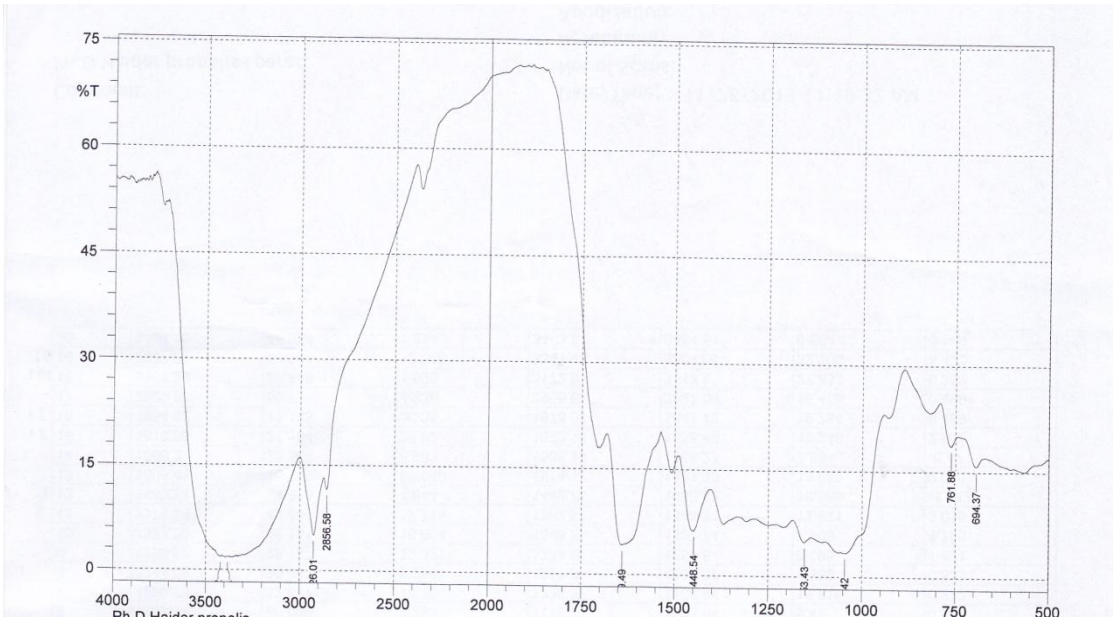

Figure 2: Fourier Transform Infra Red (FTIR) of propolis powder.

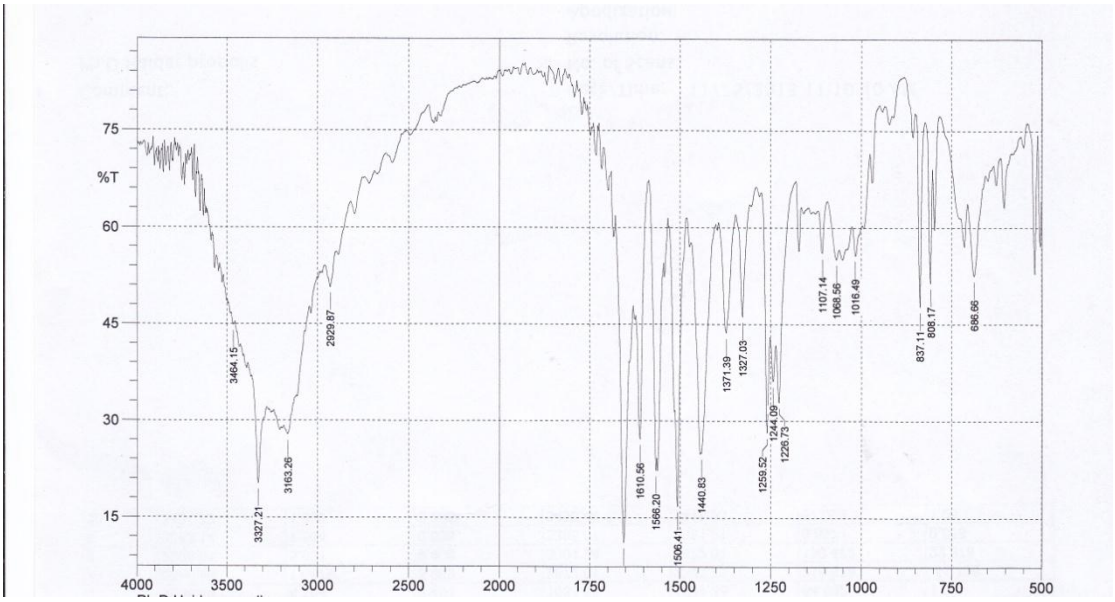

Figure 3: Fourier Transform Infra Red (FTIR) of physical mixture of paracetamol and propolis powder.

In-vitro release:

The data of in-vitro release studies are shown in the table 4. The release studies were completed up to 8 hrs for tablets forms and 2.15 hrs for capsules forms .Cumulative percentage releases with time diagram were summarized in the figures 4, 5, and 6. The cumulative percentage drug release was compared for F1, F2, F3, FM1, FM2 and FM3 in which the amount of drug is kept constant for both physical blend and matrix form prepared by solvent evaporation method(150mg).The observed percents drug release were found to be 87 %, 85.9% and 73% which is in the order of F1>F2>F3 at 5 hrs correlating with the increase in the quantity of propolis powder which restricted the release of paracetamol from the tablet forms, as well as the release of drug from F4 formula which represent tablet form without propolis was 91% at 35 min . On other hand, the results obtained for drug release of matrix tablet forms was found in the order of F1M>F2M>FM3 at 5 hrs in which the release was found to be 42.5 %, 40.8 % and 33.6 % for FM1, FM2 and FM3 respectively. The data shows that, when propolis ratio was increased, the in-vitro drug release from tablet was decreased which may be due to increased path length for diffusion of drug molecule from tablet. The release was high from tablet prepared by direct compression of physical blends as compared to matrices prepared by compression of granules of solid matrix that made by solvent evaporation method. The result attributed to the making of coating of propolis over drug particles [10]. Also the integrity of matrix tablet produced by granulation of solid matrix (prepared by solvent evaporation method) was found to be superior to tablet prepared by direct compression of physical mixtures and the drug particles found in the deeper area was released at a slower rate [19]. A similar result was obtained with capsules dosage forms. As the amount of propolis was increased, the release was decreased .The cumulative percentage drug release was in the order of FC>FMC2>FMC3 at 75 min and the release was found to be 98 %, 83.6 % and 66.7 % for FC, FMC and FMC3 formulas respectively.

The release data obtained were fitted to to zero-order (cumulative amount of drug release versus time), first-order (log cumulative percentage of drug remaining versus time), Higuchi (cumulative

percentage of release versus square root of time) and Korsmeyer-Peppas (log cumulative percentage of drug released versus log time) equation models as shown in the following equations[20].

Zero order ----------Mt = M0 + Kt .

First order ---------- ln Mt = ln M0 + Kft.

Matrix (Higuchi)----------Mt = Kh t0.5

Koresmeyer-Peppas ----------Mt / M∞=Kk tn

The model that best fitted the release data was evaluated by correlation coefficient (R^2).No lag phase could be noticed because of the minimum sampling time.

Table 4: In Vitro Release Kinetics of Paracetamol from Different Dosage Form

Formula code	Zero order R^2	First order R^2	Matrix (Higuchi) R^2	Koresmeyer-Peppas R^2	Release exponent (n)
F1	0.324929	0.45273	0.556722	0.324929	0.731949
F2	0.701143	0.805603	0.865128	0.701143	0.934344
F3	0.878572	0.945424	0.953407	0.878572	0.969682
FM1	0.839432	0.887931	0.947603	0.966805	0.622692
FM2	0.940974	0.965100	0.969991	0.978904	0.683986
FM3	0.852159	0.662359	0.944069	0.944532	0.647559

The good fit with the maximum R^2 coefficients was revealed by Higuchi models for physical blend tablet. Higuchi square root kinetic model explains, release drug from the insoluble matrix as square root of time dependent process [21]. It illustrates release of drug by diffusion mechanism. Moreover, the maximum fit for matrix tablet prepared by solvent evaporation method was illustrated by Peppas equation which described drug release from a polymeric system[21]. The values of *n* with regression coefficient for all the preparation formulas were in the range of 0.622692 to 0.969682 (n is large than 0.5) representing anomalous or nonfickian diffusion (0.5 Fickian diffusion 0.5< n <1.0 Non- Fickian diffusion)[22].

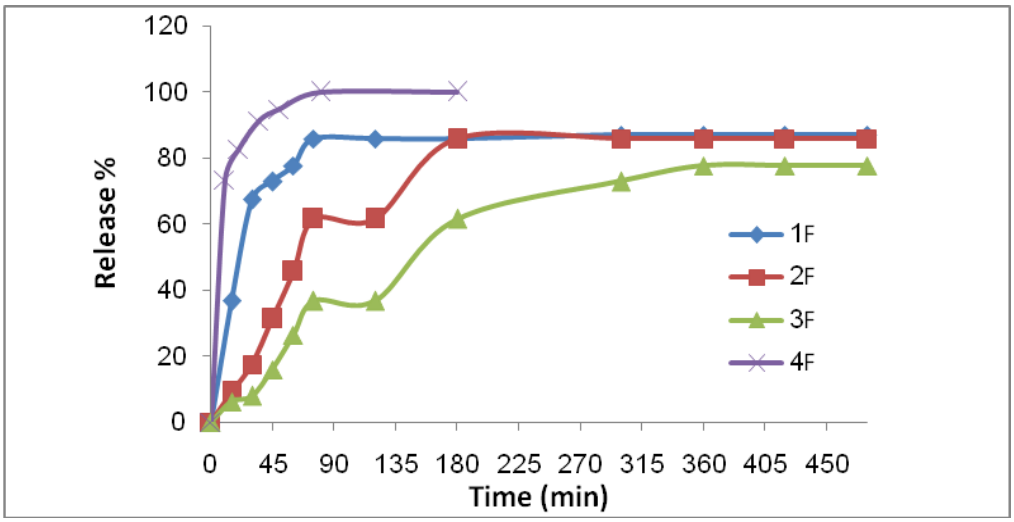

Figure 4: Comparative release profiles of paracetamol tablet made by direct compression of physical blends of drug and propolis powder.

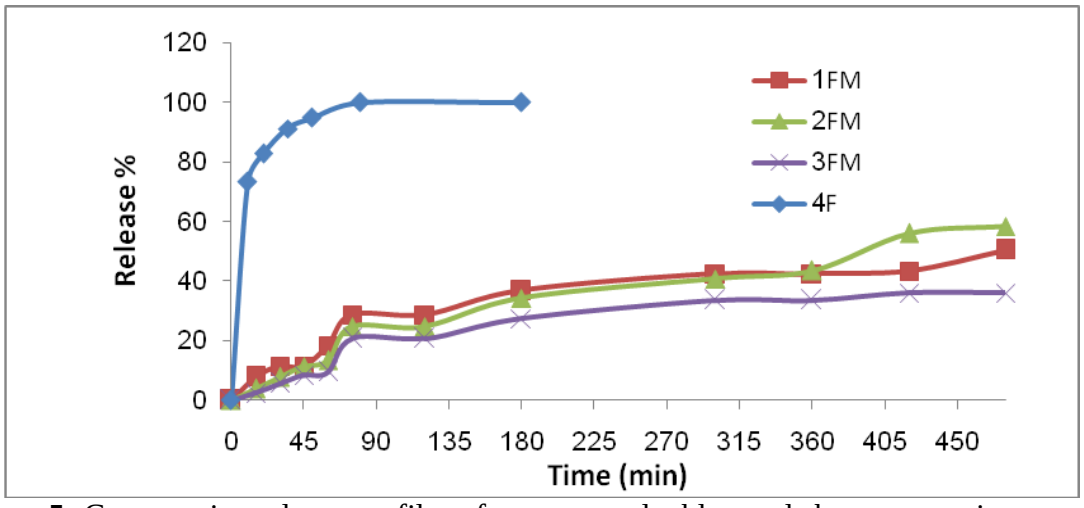

Figure 5: Comparative release profiles of paracetamol tablet made by compression granules of solid matrix of drug and propolis powder.

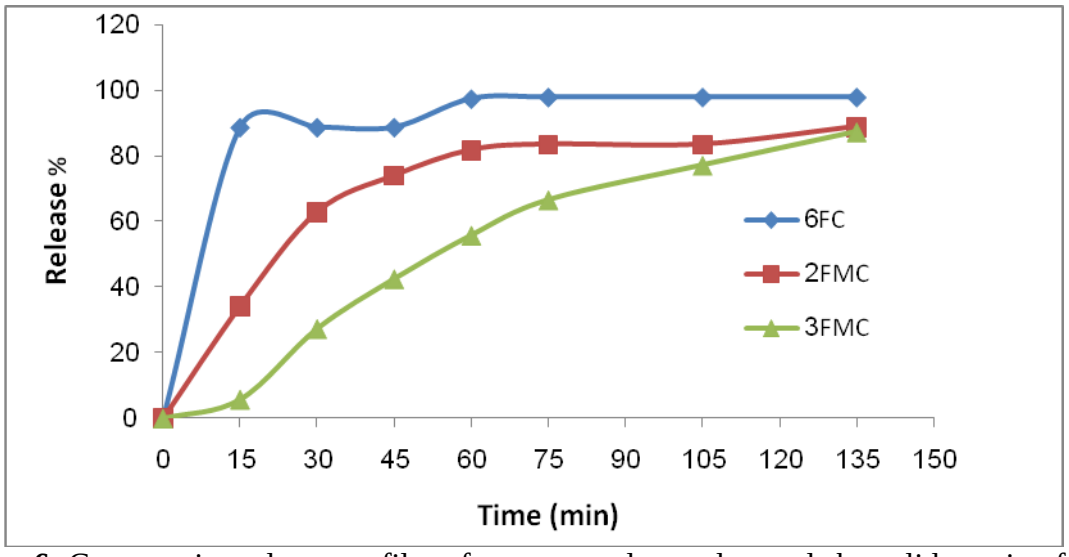

Figure 6: Comparative release profiles of paracetamol capsules made by solid matrix of drug and propolis powder.

Conclusion:

The study exhibited that propolis powder is suitable, compatible and safe material, which can be used as matrix forming agent to modify the release of paracetamol. As the amount of propolis powder was increased, the drug release rate of drug was decreased. Solid Matrix tablets of paracetamol prepared by solvent evaporation method shows retardation of drug release more efficiently than tablet prepared by direct compression of physical blend. The developed propolis matrix tablets of parcetamol may be possible for modified release of drug.

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