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Using of Sintering and Microwave Techniques to Control the Release of Trifluoperazine HCl from Wax Matrix

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الخلاصة

حضر دواء الترايفلوبيرازين هايدروكلورايد الشديد الذوبان في الماء على شكل اقراص مديدة التحرر محتوية على شمع الكارنوبه كصواغ بطريقة الكبس المباشر. استخدمت كميات مختلفة من شمع الكارنوبه لمعرفة تأثيرها على تحرر الدواء، كذلك تم استخدام تقنية التلبيد (sintering) وذلك لتثبيط تحرر الدواء من الاقراص المحتوية على شمع الكارنوبه كصواغ.

الحبيبات قبل الكبس او الاقراص بعد الكبس قد عرضت الى درجة حرارة 90 أو 120 درجة مئوية لمدة 3 او 5 دقائق. كما تم استخدام المايكروويف كتقنية للحصول على تحرر مديد للدواء من الاقراص الدوائية التي فيها شمع الكارنوبه كصواغ حيث عرضت الحبيبات قبل الكبس او الاقراص بعد الكبس الى اشعاع المايكروويف عند مستوى 600 واط ولمدة 5 دقائق.

أظهرت النتائج ان تحرر الدواء قل بصورة ملحوظة ($P<0.05$) عندما ازدادت كمية شمع الكارنوبه. من ناحية اخرى, تلبيد الحبيبات او الاقراص اظهر تثبيط ملحوظ ($P< 0.05$) لتحررالدواء عندما زيدت درجة الحراة من 90 الى 120 درجة مئوية. اضافة الى ذلك فأن تحرر الدواء لم يتاثر بمدة التلبيد بصورة ملحوظة ($P> 0.05$) عند درجة الحرارة 90 او 120 درجة مئوية. كما أن التأثير المباشر لاشعاع المايكروويف على الأقراص كان له تثبيط ملحوظ ($P<0.05$) على تحرر الدواء وخصوصا على الاقراص التي عرضت لمدة 5 دقائق حيث ان التحرر ازداد من 3 ساعات للاقراص غير المعرضة للمايكروويف إلى 6 ساعات للاقراص المعرضة للمايكروويف.

Abstract

The very water soluble drug, trifluoperazine HCl was prepared as sustained release carnauba wax matrix tablets using direct compression method. Different amounts of carnauba wax as matrix substance was used to show its effect on drug release. Also sintering as new technique was used in order to retard the drug release from carnauba wax matrix tablets; the granules before compression or the tablets after compression were exposed to 90°C or 120°C for 3 or 5 minutes. Microwave is another technique which was used to prolong the drug release from carnauba wax matrix tablets. The granules before compression

or the tablets after compression were exposed to microwave irradiation at 600 watt for 3 or 5 minutes.

The results revealed that the release of drug decreased significantly ($p<0.05$) when the when the amount of carnauba wax was increased. On the other hand, sintering of granules or tablets, exhibited a significant ($p< 0.05$) drug release retardation when the temperature was increased from 90° C to 120° C. Furthermore, non significant differences ($p> 0.05$) in drug release was shown at different time of sintering for 90°C or 120°C. The microwave irradiation directly on tablets had a significant ($p< 0.05$) retarding effect on drug release, particularly for tablet exposed to 5 minutes since the drug release prolonged from 3hr for unmicroaved tablet to 6 hr for microwaved one.

Introduction

The most common controlled delivery system is the matrix system containing dissolved or dispersed drug as tablets and granules dosage forms because of its effectiveness, low cost and ease of manufacturing [1,3]. Matrix type formulations are prepared from plastic matrices, swellable hydrophilic polymers or non-swellable lipophilic matrices [4,6].

Plastic matrices are composed from materials characterized by their capability to form insoluble, sponge-like skeletons from which the drug is released by diffusion. Examples of such materials are the acrylic/methacrylic coplymers, ethyl cellulose, polyvinyl acetate, and polyvinyl alcohol [7].

Hydrophilic matrix system such as hydroxypropyl methylcellulose (HPMC), carboxymethyl cellulose (CMC) and sodium alginate, is restricted for the highly water soluble drugs because of rapid diffusion of the dissolved drug through the hydrophilic gel network [8].

Lipophilic carriers such as carnauba wax, glycerides, stearyl alcohol and stearic acid are preferred in the preparation of sustained release matrix tablet in case of highly water-soluble drug. Various manufacturing processes using these lipophilic carriers have been used, including direct compression, hot melt extrusion, melt granulation and solvent evaporation [9].

Sintering is a new technique used to retard drug release heat is used during the preparation of solid dosage form without actually melting the materials [10]. Ethyl vinyl acetate copolymer is one of the exciepint used in sintering technique. Matrix tablets of rifampicin in ethyl vinyl acetate were prepared using direct compression and subsequent sintering technique at various temperatures. The release rate of rifampicin from ethylene-vinyl acetate matrices was inversely related to the time of sintering. Also the cumulative percent of rifampicin release decreased as the sintering temperature was increased [10].

Matrix tablets of theophylline in vinyl acetate were prepared in different drug and polymer ratios using direct compression and subsequent sintering technique at various temperatures. The release of theophylline from the

sintered tablets depended on the polymer-drug ration, temperature of sintering and time of sintering [11].

Carnauba wax found to cause the strongest retardation of drug and due to its ease and safety of application, has also been widely used as rate retarding polymer [6]. Singh et al. prepared pellets of theophylline in carnauba wax and they subjected the pellets to sintering at different temperatures and different time of interval. The release of theophylline from the pellets was retarded with increasing of the temperature of sintering and time of sintering [12].

Microwave is a new approach to control physical properties and drug delivery profiles of pharmaceutical dosage forms without the need for excessive heat, lengthy process and toxic reactants[13].Microwave were used by investigators to control the drug release from different substances such as pectin chitosan , gluten and albumin[13,14].

The release rate of metaclopramide was retarded from gluten or albumin matrices when they subjected to microwave. Application of microwave thermal energy is considered to be the mean for producing even heating throughout the matrices as compared with direct heating and thus cold be used to create uniform cross-linking thought the matrices which in turn retards the metaclopromide release [14].

In present study, the highly water soluble trifluoperazine HCl was used as model to investigates the feasibility of using sintering and microwave to retard the drug release from carnauba wax matrix. In addition drug stability and drug-wax interaction before and after exposing to sintering and microwave were studied. Finally, friability, flowbility and hardness were assessed before and after exposing to sintering and microwave.

Materials and Methods

Materials:

Trifluoperazine HCL and microcrystalline cellulose (Avicel PH 101) supplied by Samara Drug Industry (SDI). Carnauba wax and talc powder (BDH-Liverpool, England). Magnesium stearat (Barlocher , GMBH, Germany). Other materials used were of analytical grade.

Instruments:

UV Spectrophotometer (Carry UV, Varian, Australia). Hardness tester (Stokes, Monsanto, Mansanto Chemical Co. USA). Roche friablator (Moor and Wright , Sheffield LTD, England). Tablet machine (Manesty Type F3, England). Ultrasonic cleaner (VWR,Coply Scientific, England). Oven (GallenKamp, B5 ov-210, England Memmert Germany).

Methods:

Preparation of Trifluoperazine HCl Matrix Tablet

Fifteen formulas of trifluoperazine HCl matrix tablet sustained release tablet were prepared by direct compression. Formula 1-8 were prepared by

mixing trifluperazine HCl with carnauba wax and 2% of talc was added. The mixture was mixed with 1% magnesium stearate for 2 minutes and compressed directly into tablets by single punch tablet machine using 7 tons compression pressure.

The formula 1-6 were sintered at different temperature and for different time intervals, while formulas 7and 8 were exposed to microwave oven and heated for 3 and 5 minutes at a microwave power output of 600 W (table-1).

On the other hand formulas 9-15 were prepared by mixing triluoperazine HCl with carnauba wax and microcrystalline cellulose. Formulas 9-13 were sintered at different temperature and for different time intervals, whereas formulas 14and 15 were exposed to microwave oven and heated for 3 and 5 minutes at a microwave power output of 600 W (table-2).The resultant granules of formulas 9-15 were then mixed with 2% talc and 1% magnesium stearate and compressed by single punch machine using 7 tons compression pressure.

Stability and Compatibility Studies

Trifluoperaine HCl was assayed before and after exposing to sintering and microwave so that to predict the stability and compatibility of drug within the matrix tablet. Powdered tablet was shacked for 15 minutes with 400 ml of a mixture of 5 volumes of HCl and 95 volumes of water, diluted to 500 ml with same mixture, mixed and filtered. The absorbance of the filtrate was measured at the maximum at 256nm [15].

Hardness Test

The hardness of 3 tablets from each of the prepared formula was measured individually before and after exposing of formulas to sintering and microwave by using Monsanto hardness tester [16].

Friability Test

This test was done for 20 tablets, starting by weighing them and then operating the friabilator at 25 r.p.m for 4 minutes. After their revolution, they were cleaned from dust and weighed again to determine the loss in their weight[17].

Flow Properties Study

The powder was allowed to pass through a funnel and poured on a horizontal plan to form a cone. The funnel height was maintained at approximately 2-4 cm from the tip of the powder pile in order to minimize the impact of the falling powder on the tip of the cone. The base was not allowed to vibrate. Angle of repose (α) was measured by measuring the height (h) and the radius (r) of the cone; as given in the following equation [18].

$$Tana = \frac{h}{r}$$

In Vitro Release Studies

The dissolution test was carried out using USP rotating basket method. Stirring speed was maintained at 100 r.p.m. Phosphate buffer pH 6.8 was used

as a dissolution medium and maintained at 37 ±0.5°C. Samples each of 5 ml volume were withdrawn at regular intervals, filtered and assayed spectrophotometry.

The samples were assayed at 256nm to determine the amount of trifluperazine released at each time point. Dissolution studies were performed three times and the mean values were taken for a batch.

Statistical Data Analysis

The results of the experiments are given as a mean of triplicate samples ± standard deviation and were analyzed according to the one way analysis of variance (ANOVA) at the level of ($P < 0.05$).

Result and Discussion

Stability and Compatibility

The amount of trifluoperazine in unexposed and exposed tablets to sintering and microwave ranged between 97-99%. Results indicated that trifluoperazine HCl hydrochloride is adequately stable under the sintering and microwave conditions chosen for the present study and is compatible with carnauba wax, the material that comprise the bulk structure of the prepared matrices.

Hardness

The hardness of the tablet mainly affected by amount of carnauba wax and 5 min sintering at 120˚C (F2 and F6 respectively) compared to F1 as shown in figure-1. Increase amount of wax in F2 which is the substance responsible for the architecture of the tablet, increased the hardness, while in F6 the hardness increased due to the formation of strong wax network that filled any spaces between drug and wax so the hardness elevated [19].

The hardness of tablets (figure-2) resulted from sintered granules (F11-F13) also increased compared to F9, but the increasing in the hardness is more than that of directly sintered tablet (F4 and F6). This result mainly due to the presence of microcrystalline cellulose (MCC) which act as binder and improved the compressibility of the granules [20].

The increasing in the hardness of formulas F8 and F15 which are exposed to microwave irradiation for 5 minutes (figures 1 and 2) may be due to the slight cross linking in the matrix [14].

Flowbility Properties

Figure-3 show that the F13 (sintered at 120°C for 5 minutes) has the lowest angel of repose. This effect may be due to the melting of the wax and forming continuous sheet around the drug and so improved the flow properties of the resultant granules [20].

Variables Affecting Trifluoperazine HCl Release

Amount of Carnauba Wax

There is highly significant differences ($P<0.05$) in the release profile of trifluperazine HCl from F1 and F2 as shown in figure-4. As the relative

amount of wax increased in the tablet, it retards the penetration of dissolution medium by providing more hydrophobic environment and thus cause delay in release of drug from the tablet [21].

Effect of Sintering

Evaluation of the drug release before and after direct sintering on tablet revealed significant ($p < 0.5$) retardation of drug release after sintering as shown in figure-5 when F1 (without sintering) compares with F6 (sintered at 120˚C for 5 minutes). The differences arise from sintering may be due to the transformation of the wax from finely divided particles into film and sheaths cover the surface of drug and filler, result in increase surface hydrophobicity, which in turn hinder the entrance of water into the tablet[22].

Retardation may be also due to the increase in the hardness of tablet, result in increase the density and decrease porosity which caused a retardation in water penetration in to the tablet and hence decreased the release of the drug[23].

Figure-5 shows that the increasing in the temperature of sintering from 90°C to 120°C has more effect than increasing the time of sintering from 3 to 5 to the same temperature. The percent of drug release after 3 hr. was 98.8%, 96.3%, 51.1% and 50% for formulas F3, F4, F5, F6 respectively as shown in figure-6. Thus statistical calculation of ANOVA test revealed no significant differences ($P>0.05$) in the drug release percent after the increasing of time of sintering with constant temperature, while the differences in the drug release percent after the increasing of temperature with constant time of sintering was significant ($P<0.05$).

On sintering, wax particles melted and penetrated the empty spaces, forming a continuous sheet around the drug and other materials, which increased the surface area of wax and thus indicated a nearly monolithic formation. In other words, sintering increased the percentage area of drug covered, thereby decreased the exposure of the drug to the dissolution medium, and hence the release of the drug was retarded [12].

F10-F13 were prepared in different way than that for F3-F6, since CMC was added in addition sintering was done to the granules before compression to predict if the sintering by this method can retard the drug release . As in case of direct sintering to tablet, the result of sintering to granules showed that the increasing in the temperature of sintering to granules from 90°C to 120°C had more effect than increasing the time of sintering from 3 to 5 minutes at constant temperature as shown in figure-7.The retardation of drug release after sintering of granules may be due to the same reason mentioned with sintering of tablets[12].

Effect of Microwave

F7 and F8 which were exposed to microwave showed significant ($p< 0.05$) retarding effect on release rate of the trifluoperazine HCl. However, the release profile for matrices exposed for 5 minutes (F8) showed a significant decline in the rate of drug release, particularly during the late stage of the drug-

release profile as shown in figure-8. This finding is believed to be the result of slight cross-linking in the system [14], or may be due to the decreasing in the tablet porosity after exposure to microwave irradiation [24].

The microwave dielectric heating is a form of energy transferred to all parts of granules in the same time via the vibration and oscillation of molecules and particles that converted to heat promoting the jumping of particles so fill the vacant spaces [14, 25]. This effect will reduce the void volume (porosity) rather than the induce grain growth (increasing the tortousity) which accrues in the conventional sintering, where in the later there is gradual transfer of heat from the surface of the granules to the center leading to generate grains and increase the tortousity[26].

The increased tortousity has larger effect than decreased porosity on the retardation of drug release so the microwaved granules showed retardation of drug release only in the first hour where the drug release percent decreased from 84% (F9) for without microwave to 40% (F14) and 27% (F15) for 3 minutes and 5 minutes microwaving respectively (figure-9). It seen that the effect of microwave disappeared within 2 hr i.e. all formulas reached to 100% drug release within 2hr. This result may be due to the presence of microcrystalline cellulose which may counteracted the decrease in porosity, leading to bulk erosion and leaching of the drug [27].

Release kinetics

The release of the model drug was sustained over the experimental time. To elucidate the possible release mechanism, analysis of drug release data derived from the dissolution tests were fitted to the exponential equation [28].

$$M_t/M_\infty = k\, t^n$$

where Mt is the amount of drug released at time t, M∞ the nominal total amount of drug, Mt/M∞ is the fraction of drug released within the range 0.1–0.6 at time t, k is the kinetic constant that incorporates the properties of the polymeric system and the drug, and n is the diffusional exponent of the drug release that is used to characterize the transport mechanism. In the case of tablets, n = 0.45 for Case I (Fickian diffusion), 0.45 < n <0.89 for anomalous behaviour (non-Fickian swelling or eroding transport) and n≥0.89 for Case II transport.

It is obvious from table 3 that n range from 0.53 to 0.85, that's mean the release kinetic is anomalous release of both diffusion and erosion[28].

The other formulas (9, 10, 12, 14 and 15), can not be fitted to Peppas equation because of their fast release and the percent of drug released did not reach to 60%.

Conclusion

Sintering and microwave are simple and low coast techniques for preparation of wax-based sustained release tablet, since by controlling time and temperature of sintering the drug release can be controlled..

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Formula No	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
Trifluperazine	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg
Carnauba wax	100 mg	**150** mg	100 mg	100mg	100mg	100mg	100mg	100mg
Talc	2%	2%	2%	2%	2%	2%	2%	2%
Mg Stearate	1%	1%	1%	1%	1%	1%	1%	1%
3 min 90 C°			**Sintered**					
3 min 120 C°				**Sintered**				
5 min 90 C°					**Sintered**			
5 min 120 C°						**Sintered**		
Microwave 3 min							**Micro-waved**	
Microwave 5 min								**Micro-waved**

Table 1: Different formulas of trifluoperaine HCL matrix tablet.

Formula No	9	10	11	12	13	14	15
Trifluperazine	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg
Carnauba wax	70 mg	70 mg	70 mg	70 mg	70 mg	70 mg	70 mg
MCC	120 mg	120 mg	120 mg	120 mg	120 mg	120 mg	120 mg
Talc	2%	2%	2%	2%	2%	2%	2%
Mg Stearate	1%	1%	1%	1%	1%	1%	1%
3 min 90 C°		**Sintered**					
3 min 120 C°			**Sintered**				
5 min 90 C°				**Sintered**			
5 min 120 C°					**Sintered**		
Microwave 3 min						**Microw-aved**	
Microwave 5 min							**Micro-waved**

Table 2: Different formulas of trifluoperaine HCL matrix tablet.

Formula	R^2	n	K (hr^{-1})
F1	1	0.585	0.500035
F3	0.9654	0.6744	0.339703
F4	0.9955	0.5716	0.204927
F5	0.9852	0.691	0.294103
F6	0.9919	0.6554	0.156819
F7	1	0.5334	0.380014
F8	0.9946	0.8513	0.236211
11	0.9261	0.5346	0.2795
13	0.9736	0.5983	0.2464

Table 3: statistical results of Korsmeyer – Peppas equation.

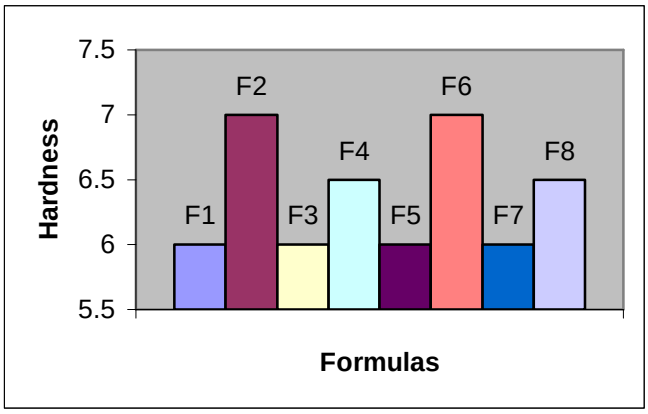

Figure 1: The effect of formulation process on the hardness of formulas 1-8

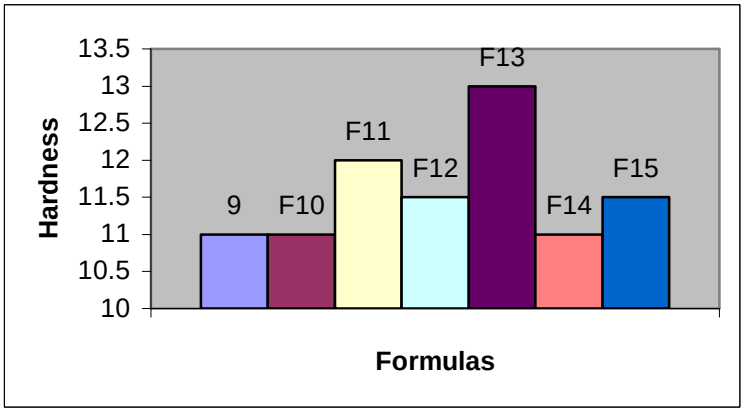

Figure 2: The effect of formulation process on the hardness of formulas 9-15

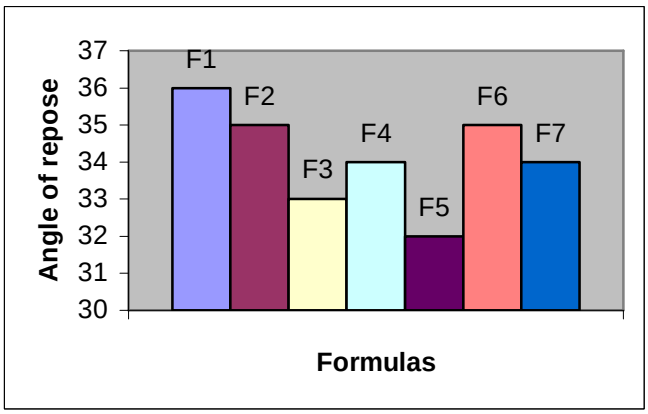

Figure 3: The effect of sintering on the angle of Repose

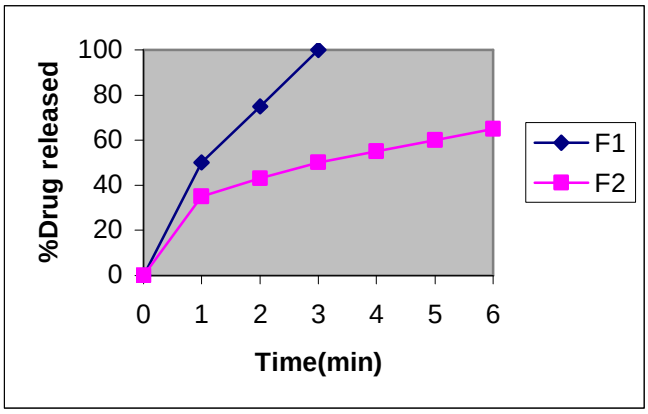

Fig 4: The effect of amount of carnauba wax on the release profile of trifluperazine HCl.

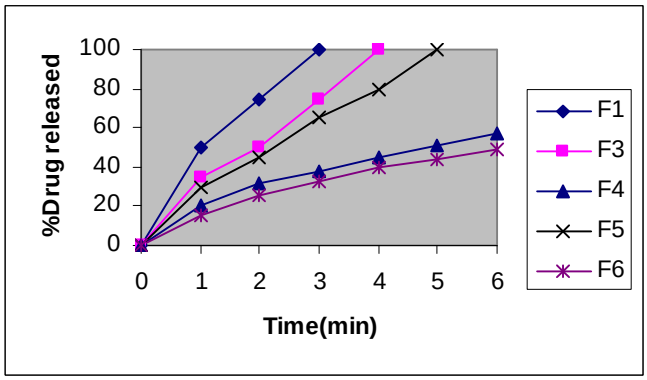

Figure 5: The effect of sintering on the release profile of trifluperazine HCl.

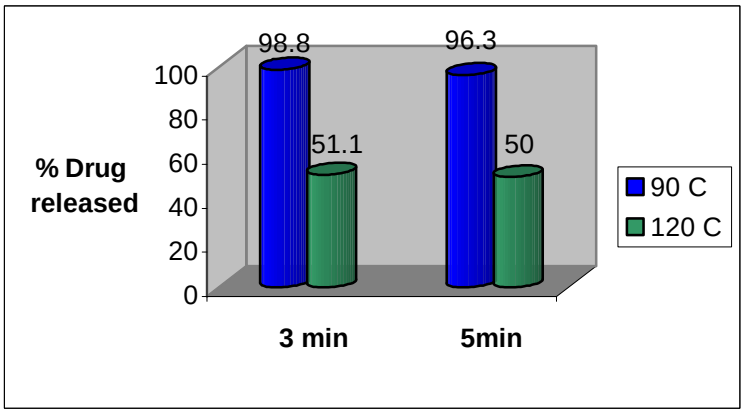

Figure 6: The effect of degree and time of sintering on the percent of drug release after 3 hr.

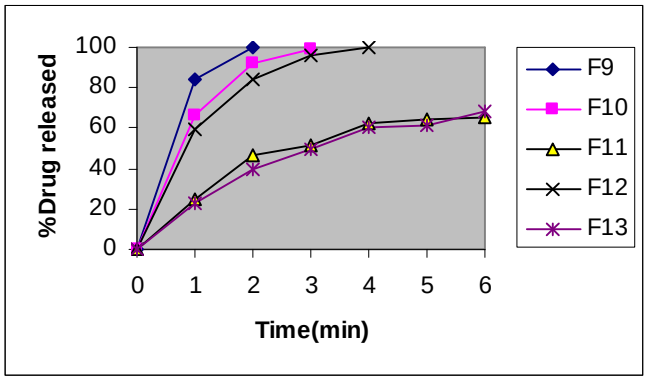

Figure 7: The effect of sintering on release profile of trifluperazine HCl.

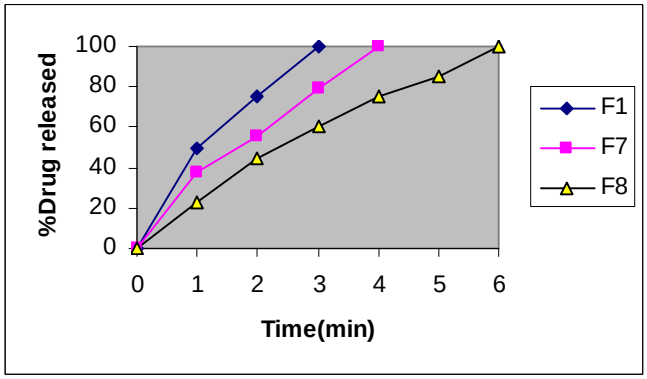

Figure 8: The effect of microwave irradiation on the release profile of trifluperazine HCl

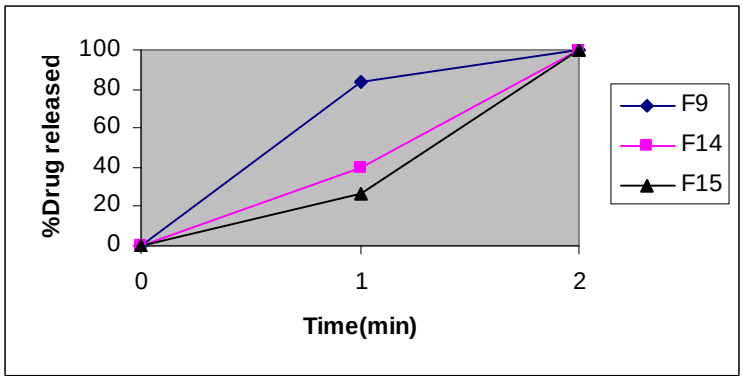

Figure 9: The effect of microwave irradiation on the release profile of trifluperazine HCl.