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EVALUATION OF IN VITRO DISSOLUTION PROFILE COMPARISON METHODS OF SUSTAINED RELEASE TRAMADOL HYDROCHLORIDE LIQUISOLID COMPACT FORMULATIONS WITH MARKETED SUSTAINED RELEASE TABLETS

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The aim of present work was preparation and evaluation of sustained release liquisolid compact formulations of tramadol hydrochloride. Comparison of dissolution profiles of prepared compacts with marketed preparation was also done. Liquisolid sustained release formulations were prepared by using HPMC K4M as adjuvant for sustaining release. Precompression studies such as flow properties were also carried out. Liquisolid compacts were evaluated by hardness, friability, and in vitro dissolution studies. Comparison of dissolution profiles was carried out by using model independent, model dependent and statistical approach. The prepared liquisolid compacts are new dosage forms showing more sustained release behavior as compared to marketed sustained formulations. Dissolution profile followed Peppas model as "best fit" model. Two Way ANOVA results showed significant difference in dissolution profiles. This systematic approach to the formulation was found to be useful in analyzing sustained release of tramadol hydrochloride. The application and evaluation of model dependent methods are more complicated. These methods give acceptable model approach which is indication of true relationship between percent drug release and time variables, including statistical assumptions.

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1. Introduction

Sustained release dosage form is mainly designed for maintaining therapeutic blood or tissue levels of the drug for extended period of time with minimized local or systemic adverse effects. Economy and greater patient compliance are other advantages [1]. In recent years, clinical studies on Tramadol Hydrochloride have demonstrated that this drug is an effective agent for moderate to severe chronic pain [2-5]. The half-life of the drug is about 5.5 hours and the usual oral dosage regimen is 50 to 100 mg every 4 to 6 hours with a maximum dosage of 400 mg/day [6]. To reduce frequent administration of dosage form and to improve patient compliance, a sustained-release formulation tramadol is desirable. The drug is freely water soluble and hence judicious selection of release retarding excipients is necessary to achieve a constant in vivo input rate of the drug. Various approaches have been used by researchers to sustain drug release in the form of tablets [7-9].

Liquisolid system is novel technique developed by Spireas et al [10-11]. "Liquisolid systems" involves conversion of liquid lipophilic drugs or water insoluble solid drugs dissolved in non-volatile solvent and this liquid medication can be converted into free-flowing, non adherent, dry looking, and readily compressible powders with use of carrier and coating materials. In case of water soluble drugs, the sustained release can be obtained [12]. The term liquisolid compacts as described by Spireas et.al [10-11] indicates that immediate or sustained release tablets or capsules that are prepared using the technique of "liquisolid systems" combined with inclusion of appropriate adjuvants required for tabletting or encapsulation such as lubricants and for rapid or

sustained release action, such as disintegrants or binders, respectively[10]. Low cost, simple formulation technique and capability of industrial production serve to be advantages of this technique[13].

In the present study, Hydroxy Propyl Methyl Cellulose (HPMC) K4M was used as adjuvant for sustaining drug release from liquisolid compacts. Avicel PH 102 and Aerosil 200 were used as carrier and coating materials, respectively. Precompression studies such as determination of angle of repose, Hausner's ratio, Carr's index and stereomicroscopic analysis was also studied. The discrimination of release profiles was compared with marketed tablets of Tramadol hydrochloride using model independent method f_2 and statistical approach Two Way Repeated measures ANOVA. Model fitting was also done for different models such as zero order, first order, Hixon-Crowell, Peppas and Matrix models. New formulation mathematical model as described by Spireas et al. [10] was used to calculate appropriate amounts of carrier and coating materials based on new fundamental properties of powder called flowable liquid retention potential (Φ value) and compressible liquid retention potential (Ψ number) of powder ingredients (Previously determined by Spireas et al.). [10-11]

2. Materials and methods

2.1 Materials

Tramadol was kindly gifted by Panacea Biotec (India). HPMC K4M, Avicel PH 102 and Aerosil 200 were kindly gifted by Okasa Pharmaceuticals (India). Propylene glycol was purchased from Loba Chemie (India). All other reagents and chemicals were of analytical grade.

2.2 Application of mathematical model for design of liquisolid compacts

The formulation design of liquisolid systems was done in accordance with new mathematical model described by Spireas et al [10]. In this study, propylene glycol was used as liquid vehicle; Avicel PH 102 and Aerosil 200 were used as the carrier and coating materials, respectively. Concentration of the drug in propylene glycol was taken as 10, 20, and 30 g% and the carrier: coat ratios were varied from 30, 40 and 50. According to new theories, the carrier and coating powder materials can retain only certain amounts of liquid while maintaining acceptable flowability and compressibility.

The excipients ratio *R* of powder is defined as,

$$R = Q / q \tag{1}$$

Where *R* is the ratio between the weights of carrier (Q) and coating (*q*) materials present in the formulation.

Liquid load factor (L_f) is defined as the ratio of the weight of liquid medication (W) over the weight of the carrier powder (Q) in the system, which should be possessed by an acceptably flowing and compressible liquisolid system. i.e,

$$L_f = W / Q \tag{2}$$

Flowable liquid retention potential (Φ value) of powder excipients was used to calculate the required ingredient quantities. Therefore, powder excipients ratios *R* and liquid load factors L_f of the formulations are related as follows:

$$L_f = \boldsymbol{\Phi} + \Phi\,(1 / R) \tag{3}$$

Where, $\boldsymbol{\Phi}$ and Φ are the Φ values of carrier and coating materials, respectively.

Hence to calculate the required weights of the excipients used, first from Eq. (3), Φ and Φ are constants, therefore, according to ratio of carrier / coating materials (*R*), L_f was calculated.

By use of above mathematical model, liquisolid compacts were formulated as follows:

Table 1 Formulation design of liquisolid compacts.

Formulation Batch Code	Drug concentration in Propylene glycol (%w/w)	*R*	L_f	Avicel PH 102 (mg) (Q = W/L_f)	Aerosil 200 (mg) (*q*= Q/*R*)	HPMC K4M (mg)
F1	10	30	0.270	197.5	6.58	100
F2		40	0.243	219.46	5.48	150
F3		50	0.226	235.97	4.71	200
F4	20	30	0.270	395.03	13.10	100
F5		40	0.243	438.93	10.97	150
F6		50	0.226	471.94	9.43	200
F7	30	30	0.270	592.59	19.75	100
F8		40	0.243	658.43	16.46	150
F9		50	0.226	707.96	14.15	200

2.3 Determination of solubility

Saturated solutions were prepared by adding excess of tramadol to the propylene glycol and shaking on the shaker for 48 h at 25 ^{0}C under constant vibrations. The solutions were filtered through a 0.45 micron filter, diluted with in water and analyzed by Shimadzu 1700 UV-Vis spectrophotometer at 271.5 nm against blank sample (blank sample was solution containing same concentration of used without drug). Three determinations were carried out for each sample to calculate the solubility of tramadol.

2.4 Preparation of liquisolid compacts

Calculated quantities of Tramadol hydrochloride and propylene glycol was accurately weighed in 20 ml glass beaker and then heated to 180 ^{0}C. Resulting hot medication was incorporated into calculated quantities of carrier, coating materials. Mixing process is carried out in three steps as described by Spireas et al [10]. During first stage, system was blended at an approximate mixing rate of one rotation per second for approximately one minute in order to evenly distribute liquid medication in the powder. In second stage, the liquid/powder admixture was evenly spread as a uniform layer on the surfaces of mortar and left standing for approximately 5 minutes to allow drug solution to be absorbed in the interior of powder particles. In third stage, powder was scraped off the mortar surfaces by means of aluminum spatula. Then HPMC K4M was added to this mixture and blended with mortar. This gives final formulation which was compressed into tablets using single punch tablet compression machine.

2.5 Precompression studies

Flow properties

Flow properties of liquisolid formulation were studied by angle of repose, Carr's index and Hausner's ratios [14]. Each analysis was carried out in triplicate. Bulk density measurements were carried by placing fixed weight of powder in graduated cylinder and volume occupied was measured and initial bulk density was calculated. Cylinder is then tapped at a constant velocity till a constant volume was obtained. Then tapped density was calculated. Angle of repose was calculated by fixed height cone method. All studies were done in triplicate.

2.6 Evaluation of liquisolid compacts

The *hardness* of liquisolid compacts was determined by using Pfizer Hardness Tester (Pfizer). Mean hardness of each formula was determined. The *friability* of prepared liquisolid compacts was determined using Digital tablet friability tester (Roche).

2.7 In vitro drug release studies

The studies were done on six station USP dissolution apparatus I (LabIndia). All batches of tablets were evaluated (n=3) using 900 ml of sequential gastrointestinal release medium, i.e. 0.1N hydrochloric acid (pH 1.2) for first two hours, acetate buffer of pH 4.5 for next 2 hrs and then phosphate buffer of pH 7.4 for remaining 6 hours. Temperature was maintained at 37 ± 0.5°C throughout the study and stirring at 50 rpm was carried out. Samples were collected periodically, filtered through 0.45 micron filter and replaced with dissolution medium. After filtration through Whatman filter paper 41, concentration of Tramadol hydrochloride was determined spectophotometrically at 271.5 nm (Shimadzu 1700 UV-Vis Spectrophotometer). Actual amount of released drug was determined from the calibration curve (n=3).

2.7.1 Model independent approach

According to US FDA guidance for dissolution data equivalence, model independent approach is recommended. This involves use of similarity factor (f_2) which provides simple means to compare the data. The similarity factor (f_2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between the two curves.

$$f_2 = 50 \bullet \log \{[1+(1/n)\sum_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \bullet 100\} \quad (4)$$

Where *n* is the number of time points, R is the dissolution value of the reference at time t, and T is the dissolution value of the test at time t.

2.7.2 Model dependent methods

The drug release from liquisolid compacts was analyzed by various mathematical models such as zero order, first order, Hixon-Crowell, Peppas, Hixon-Crowell and Matrix models.

2.7.3 Statistical Methods

Repeated measures Two Way ANOVA was used to determine how dissolution is affected by two factors. The percentage dissolved was dependent variable and time was a repeated factor.

3. Results and discussion

3.1 Application of new mathematical model for design of liquisolid systems

Tramadol hydrochloride was selected as model drug for this study as a suitable candidate for sustained release. Liquisolid hypothesis of Spireas et al. [10] states that drug candidate dissolved in liquid nonvolatile vehicle and incorporated into carrier material having porous structure and closely matted fibers in its interior, phenomenon of both adsorption and absorption occurs. This concludes that drug in the form of liquid medication is absorbed initially in the interior of particles of carrier and after saturation of this process it gets adsorbed into internal and external surfaces of carrier. Coating materials such as Aerosil 200 which have high adsorptivity and grater surface area lead the liquisolid systems desirable flow properties [15].

Mathematical model equation for Avicel PH 102 and Aerosil 200 in propylene glycol can be given according to values of Phi (Φ) as given by Spireas et.al [10-11].

$$L_f = 0.16 + 3.31\ (1 / R) \quad (5)$$

Based on this equation, L_f is calculated by using different *R* values.

3.2 Solubility of tramadol hydrochloride in propylene glycol

Determination of solubility is most important aspect in formulation of liquisolid systems. This may contribute to formation of molecular dispersion of the drug in non-volatile solvent such as propylene glycol. The solubility of tramadol in propylene glycol was found to be 6.254 ± 0.44 g/10ml.

3.3 Precompression studies for liquisolid systems

Flow properties

Flow properties are the important concern in the formulation and industrial production of tablet dosage form. Results of measurements such as angle of repose, Carr's index, and Hausner's ratio are represented in the Table 2. Angle of repose is characteristic to the flow rate of powder. In general, values of angle of repose $\geq 40^0$ indicate powders with poor flowability [14]. The results are according to this statement. Also results of Carr's index and Hausner's ratio show good flow behavior.

Table 2 Results of flowability parameters of liquisolid powder systems for different formulation batches

Formulation Batch Code	Average Angle of Repose (θ) ± SD	Average Carr's index (%) ± SD	Average Hausner's Ratio ± SD
F1	40.61 ± 0.54	19.29 ± 0.15	1.23 ± 0.01
F2	38.97 ± 0.57	19.63 ± 0.24	1.26 ± 0.01
F3	38.76 ± 0.24	21.31 ± 0.19	1.28 ± 0.01
F4	39.62 ± 0.52	20.21 ± 0.18	1.24 ± 0.01
F5	38.49 ± 0.97	22.40 ± 0.80	1.27 ± 0.01
F6	38.02 ± 0.12	25.40 ± 0.31	1.30 ± 0.01
F7	39.19 ± 0.46	21.47 ± 0.23	1.27 ± 0.02
F8	38.56 ± 0.11	23.80 ± 0.15	1.32 ± 0.01
F9	37.40 ± 0.32	25.30 ± 0.16	1.34 ± 0.01

3.4 Evaluation of liquisolid compacts

Results of hardness, friability, disintegration time are represented in Table 3. There should be certain amount of strength or hardness and resistance to friability for the tablet, so that tablet should not break during handling. However, it has also effect on drug dissolution. Average *hardness* of liquisolid tablet ranges from 5.11 ± 0.25 to 6.44 ± 0.42 kg/cm^2. Compactness of tablet may be due to hydrogen bonding between Avicel PH 102 molecules [16]. As propylene glycol is an alcoholic compound, it might show hydrogen bonding due to presence of hydroxyl groups and may contribute to compactness of compacts. *Friability* studies of liquisolid compacts are in the range of 0.133 % to 0.278%. This indicates that acceptable resistance is shown by liquisolid compacts to withstand handling.

Table 3 Results of Hardness and friability tests of sustained release liquisolid tablet formulations

Formulation Batch Code	Average Hardness (kg/cm^2) ± SD	Percentage fines obtained during friability test (%)
F1	5.11 ± 0.25	0.174
F2	5.78 ± 0.15	0.210
F3	6.14 ± 0.38	0.256
F4	5.74 ± 0.20	0.192
F5	5.96 ± 0.37	0.244
F6	6.26 ± 0.15	0.278
F7	6.32 ± 0.34	0.143
F8	6.44 ± 0.42	0.267
F9	6.29 ± 0.29	0.133

3.5 In vitro dissolution studies

In preparation of liquisolid compacts, liquid medications containing drug were adsorbed on the surface of carrier materials. When this system is exposed to the dissolution medium, drug located onto the surface of compacts dissolves fast and diffuses into dissolution medium. This can be assumed to be the cause of the burst release effect observed. The concentration of drug in liquid medication is an important aspect as it affects drug release. As it was proved previously, increase in drug concentration in liquid medication, lower drug release rate would observe. It was due to fact that at higher drug concentration, drug tends to precipitate within silica (Aerosil 200) pores. This fact was also supported by Javadzadeh et al. [17]. At higher amount of Aerosil 200 (Batch F9), drug release was found to be retarded as compared to other batches. Increase in concentration of HPMC K4M might be responsible to get sustained effect. This is reflected in batches F3, F6, and F9. However, marketed sustained release tablets showed faster release as compared to liquisolid sustained release formulations.

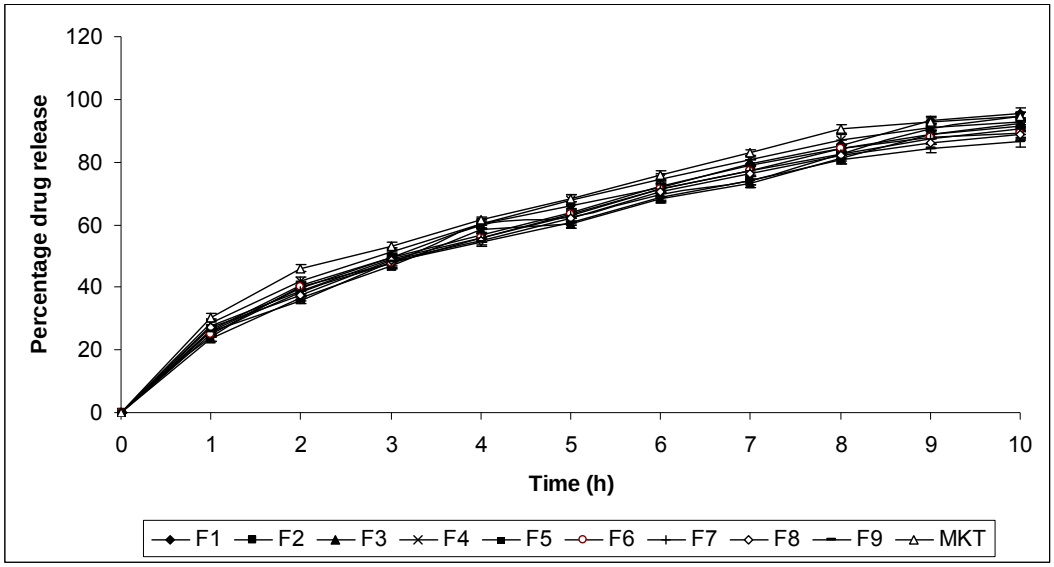

Fig. 1 In vitro dissolution profile of sustained release tramadol hydrochloride liquisolid compacts (F1-F9) compared with marketed formulation (MKT)

3.5.1 Model independent methods

The model independent method such as similarity factor (f_2) provides simple way to

compare dissolution data. US FDA guidance proposes that f_2 values of 50 – 100 indicate equivalence in dissolution profiles. Table 4 shows f_2 values of all the batches. Although dissolution profile seems to be equivalent with that of marketed tablet, discrimination in f_2 values of batches F1 to F3 might be due to lower concentration of drug present in the formulations. Other batches show f_2 values >50, which indicates similarity in dissolution profile.

Table 4 Similarity factor (f_2) values of liquisolid compacts compared with marketed tablet

Comparison	f_2	Dissolution profile
F1 and MKT	24.52	Dissimilar
F2 and MKT	25.96	Dissimilar
F3 and MKT	11.90	Dissimilar
F4 and MKT	63.30	Similar
F5 and MKT	60.11	Similar
F6 and MKT	56.11	Similar
F7 and MKT	83.12	Similar
F8 and MKT	69.33	Similar
F9 and MKT	64.79	Similar

3.5.2 Model dependent methods

Although model independent methods are simple and easy to apply, they lack scientific justification [18-20]. Different models of dissolution profile comparison were used (Table 5 and 6). The results of these models indicate all liquisolid compacts follow Peppas model as "best fit model". This is due to previously proved fact depending on R^2 value obtained from model fitting [21]. T_{50} % of all the formulations was also determined which indicate that batches F3 and F9 showed more release retarding effect. It is thus found that T_{50} % value increases as concentration of HPMC K4M increases. Korsmeyer - Peppas release exponent (n) values of all liquisolid compacts are greater than 0.5 indicating non - Fickian diffusion i.e. initially there is rapid release the reason of which is previously explained.

Table 5 Parameters and determination coefficients of release profile from sustained release liquisolid compacts (F1-F5)

Model	Parameter	F1	F2	F3	F4	F5
Zero order	R^2	0.9121	0.9196	0.9223	0.8782	0.8969
	k	11.129	10.788	10.567	11.177	10.843
First order	R^2	0.9684	0.9655	0.9764	0.9930	0.9933
	k	-0.262	-0.240	-0.223	-0.252	-0.232
Matrix	R^2	0.9975	0.9954	0.9953	0.9991	0.9986
	k	29.885	28.931	28.325	30.155	29.182
Peppas	R^2	0.9990	0.9973	0.9977	0.9991	0.9988
	k	26.469	25.031	24.307	29.121	27.061
Hixon-Crowell	R^2	0.9923	0.9889	0.9908	0.9909	0.9921
	k	-0.062	-0.058	-0.055	-0.061	-0.057
Korsmeyer-Peppas release exponent (n)	n	0.5660	0.5784	0.5828	0.5197	0.5413
T_{50}% (h)		3.1	3.3	3.4	2.8	3.1

Table 6 Parameters and determination coefficients of release profile from sustained release liquisolid compacts (F6-F9) and marketed sustained release tablet

Model	Parameter	F6	F7	F8	F9	MKT
Zero order	R^2	0.9004	0.8936	0.8964	0.8967	0.8636
	k	10.679	10.680	10.513	10.297	11.452
First order	R^2	0.9959	0.9941	0.9960	0.9967	0.9867
	k	-0.221	-0.222	-0.212	-0.200	-0.274
Matrix	R^2	0.9976	0.9991	0.9986	0.9982	0.9983
	k	28.725	28.756	28.293	27.712	30.941
Peppas	R^2	0.9978	0.9994	0.9989	0.9983	0.9976
	k	26.042	27.512	26.685	25.797	31.230
Hixon-Crowell	R^2	0.9902	0.9904	0.9891	0.9864	0.9892
	k	-0.056	-0.056	-0.054	-0.052	-0.065
Korsmeyer-Peppas release exponent (n)	n	0.5538	0.5235	0.5314	0.5388	0.4954
T_{50}% (h)		3.2	3.1	3.3	3.4	2.6

Different models were characterized based on the plots which are shown in Fig 2-5.

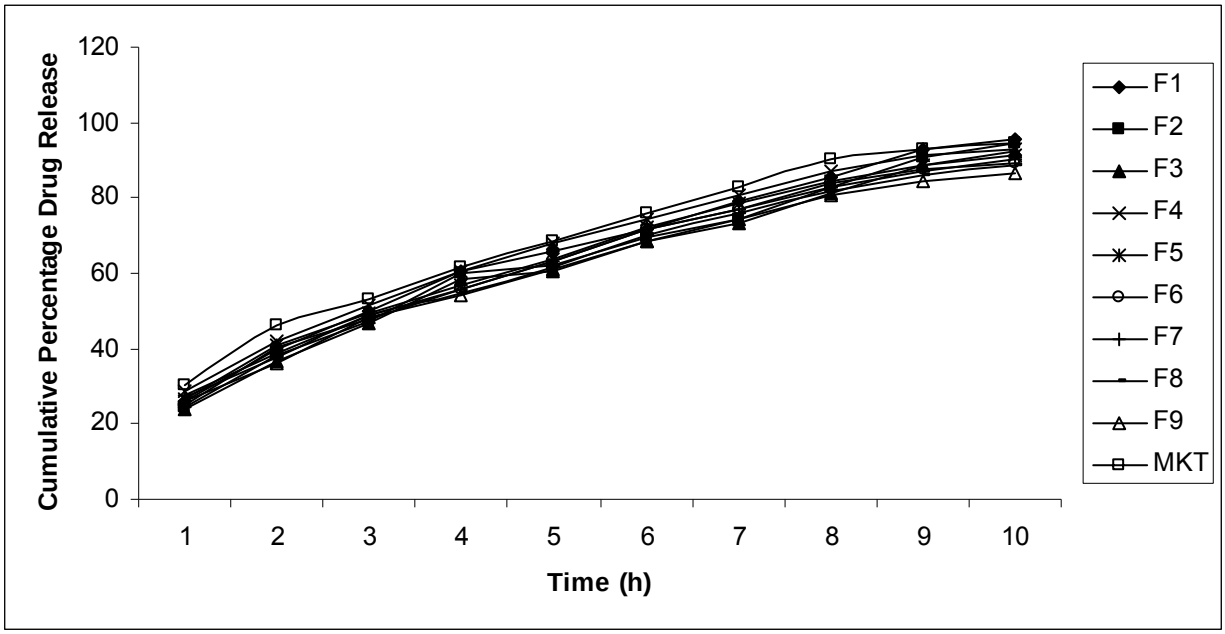

Fig.2 Zero order plot for liquisolid compacts compared with marketed formulations

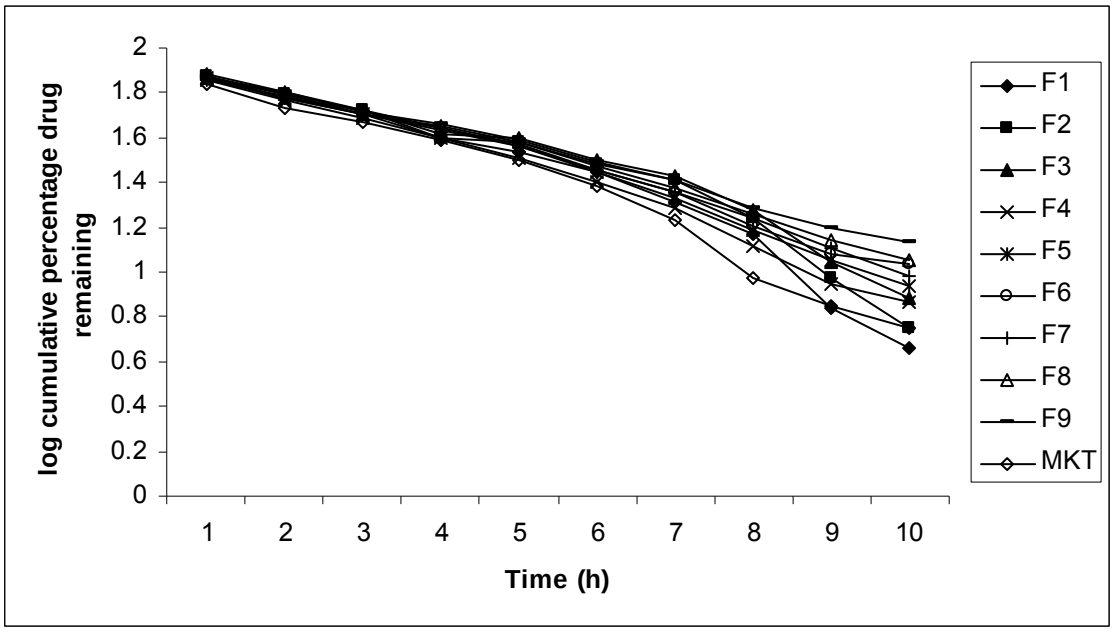

Fig. 3 First order plot for liquisolid compacts compared with marketed formulations.

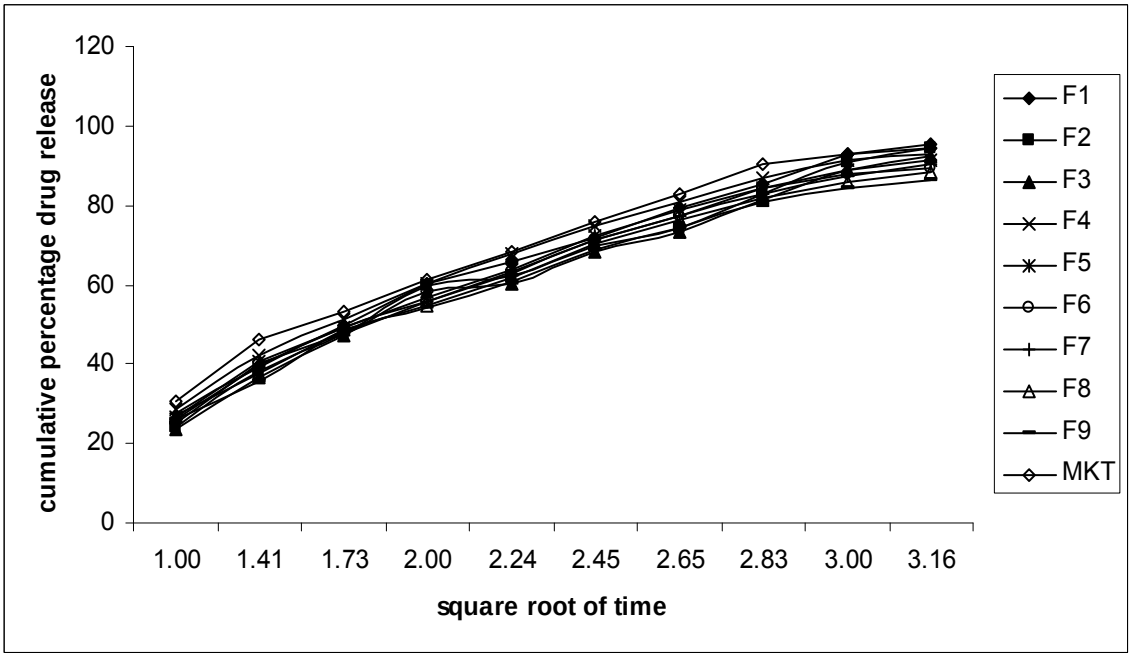

Fig.4 Higuchi plot for liquisolid compacts compared with marketed formulations

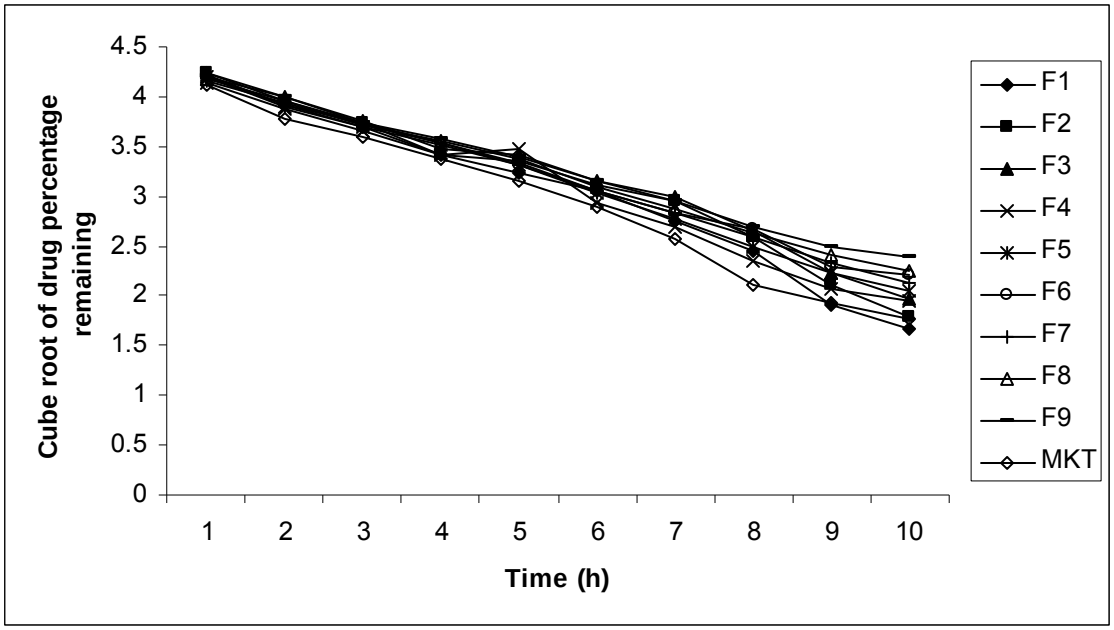

Fig. 5 Hixon-Crowell plot for liquisolid compacts compared with marketed formulations

3.5.3 Statistical methods

Statistical methods based on ANOVA are most simple ways to determine discrimination in dissolution profiles. Statistically significant difference was observed in Two Way ANOVA studies (Table 7). It was confirmed due to fact that P value is <0.0001.

Table 7 Results of Two Way ANOVA

Source of Variation	Degrees of freedom	Sum of squares	Mean squares	F value
Column factor	9	441.4	49.05	21.58
Row factor	10	81150	8115	3570.52
Residual (error)	90	204.6	2.273	
Total	109	81800		

4. Conclusion

The present work showed that liquisolid compacts technique can be effectively used for preparation of sustained release matrices of water soluble drugs such as Tramadol hydrochloride. Propylene glycol was used as liquid vehicle. Drug release profiles on model fitting follow Peppas model as best fit model which indicates drug release from sustained release dosage forms. Among the models used for dissolution profile comparison, it was concluded that model independent methods were found to be very simple, but discrimination between dissolution profiles can be found using model dependent approach.

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