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Research Article

DEVELOPMENT AND EVALUATION OF SUSTAINED RELEASE TRAMADOL MATRIX TABLET BASED ON XYLOGLUCON

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ABSTRACT

The basic goal of therapy is to achieve a steady state blood level that is therapeutically effective and non-toxic for an extended period of time.A sustained release system includes any delivery system that achieves slow release of the drug over an extended period of time. The aim was to determine the release-modifying effect of carboxymethyl xyloglucan for oral drug delivery. Sustained release matrix tablets of tramadol HCl prepared by non-aqueous wet granulation techniques with DCP as a diluent. The dried blends were compressed with other necessary excipients. The tablets were evaluated for hardness, thickness, drug content uniformity, *in vitro* drug release studies for 24 hours (*USP* dissolution apparatus II, 100 rpm, 37±0.5ºC), swelling studies and *in vivo* performance of the matrix tablet. HPMC K100M was used to prevent the burst effect. While other tableting excipients used were DCP, talc, magnesium stearate and PVP K30 was used as a binder. Levels were decided from the observations of the *in vitro* evaluation of the trial batch formulation. Simplex lattice mixture design was used to find out the optimum formulation. Seven batches were formulated as per the coded levels of the design. *In vitro* evaluations were performed on the optimization batches. Correlation between independent variables and dependent variables were. Correlation between independent variables and dependent variables were determined form the 3D graphs and contour plots. The design expert software suggested optimum formulation based on the desirability and desired acceptance criteria. The dissolution the polymer carboxymethyl xyloglucan and HPMC K100M had significant effect on drug release from the tablet. Polynomial mathematical models, generated for various response variables using multiple regression analysis, were found to be statistically Significant ,the statistical models developed for optimization were found to be valid.

Keywords: xyloglucan ,matrix tablet, HPMC, Sustained release, PVP K-30,Tramadol HCL.

INTRODUCTION

Oral route is the most preferred route for administration of drugs. Tablets are the most popular oral formulation available in the market and preferred by the patients and physicians alike. In long term therapy for the treatment of chronic disease conditions, Conventional formulations are required to be administered in multiple doses and therefore have several disadvantages. The primary benefit of a sustained release dosage form compared to a conventional dosage form is the uniform drug plasma concentration and therefore uniform therapeutic effect. Over the past two decades, sustained release dosage forms have made significant progress in terms of clinical efficacy and patient compliance. Matrix devices due to their chemical inertness, drug embedding ability and drug release character have gained steady popularity for sustaining the release of a drug.[1,9]

Hydrophilic matrices are interesting option when developing an oral sustained release formulation. The drug release from such matrices can be controlled through their physical properties. Polysaccharides are the choice of materials among the hydrophilic polymers used, because they are nontoxic and acceptable by the regulating authorities. The various polysaccharides used in drug delivery

applications are cellulose ethers, xanthan gum, locust bean gum and guar gum. Another natural polysaccharide Tamarind seed polysaccharide (TSP) or Xyloglucan obtained from the seed kernel of Tamarindus indica, possesses properties like high viscosity, broad pH tolerance, noncarcinogenicity, mucoadhesive nature, and biocompatibility. It is used as stabilizer, thickener, gelling agent, and binder in food and pharmaceutical industries. The tamarind seed polysaccharide constitutes about 65% of the tamarind seed components.[2-6]

Tramadol, a synthetic opioid of the aminocyclohexanol group, is a centrally acting analgesic with weak opioid agonist properties. 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. To reduce the frequency of administration and to improve patient compliance, a sustained-release formulation of tramadol is desirable.The drug is freely soluble in water and hence judicious selection of release retarding excipients is necessary to achieve a constant *in vivo* input rate of the drug. The most commonly used method of modulating the drug release is to include it in a matrix system. The major objective of the present investigation was to develop a sustained-release drug delivery system.[8]

MATERIALS AND METHODS

Carboxymethyl xyloglucan (CM-xyloglucan) was procuredfrom Encore Natural Polymer Private Limited, Ahmedabad. HPMC (K100 M), dicalcium phosphate were purchased from SD Fine Chemicals Ltd (Mumbai, India). PVP K-30 was procured from Loba Chemicals (Mumbai, India). Tramadol HCl was a gift sample fromRantus Pharma Ltd (Hyderabad). All the other chemicals used were of high analytical grade.

Preparation of Matrix Tablet

Matrix tablets, each containing 100 mg of Tramadol HCl, were prepared. For determining levels of carboxymethyl xyloglucan, initial trial batches with different concentrations of carboxymethylxyloglucan were prepared and evaluated for physicochemical properties of formulation and dissolution studies. In the trial runs, carboxymethyl xyloglucan concentration was varied from 50 to 250 mg. It was observed that as the concentration of carboxymethyl xyloglucan increased, the retarding effect of the formulation also increased, but a phenomenon of burst effect was prominently seen in all the formulations (Figure 1). Hence, to prevent the burst effect HPMC K100M was used. The quantities of other ingredients were kept constant, that is, DCP at 20 mg. Magnesium stearate and talc at 5 mg were used as a lubricant and a glidant, respectively. Different tablet formulations were prepared by wet granulation technique. All the powders were passed through a sieve of 80 mesh size. Required quantities of drug, polymer, and dicalcium phosphate were mixed thoroughly and a sufficient volume of granulating agent (isopropyl alcohol solution of PVP K-30) was added slowly. After enough cohesiveness was obtained, the mass was sieved through 22/44 mesh. The granules were dried at room temperature. Once dry, the granules retained on 44 mesh were mixed with 15% of fines (granules that passed through 44 mesh). Talc and magnesium stearate were finally added as glidant and lubricant, respectively. The tablets were compressed (10 mmdiameter, flat punches) using a tablet compression machine, Mini Press-Jyoti. Each tablet contained 100 mg of tramadol HCl and other pharmaceutical ingredients. Prior to the compression, the granules were evaluated for several tests.[1,20] **(Table 1: Composition of F1 to F7 formulation)**

Formulation of granules by wet mixing

All excipient are well mixed in pestal motor then Povidone, which is a polyvinyl pyrrolidone (PVP), is dissolved in water or solvent and added to the process. When PVP and a solvent/water are mixed with powders, PVP forms a bond with the powders during the process, and the solvent/water evaporates (dries). Once the solvent/water has been dried and the powders have formed a more densely held mass, then the granulation is milled. This process results in the formation of granules.[1,20]

Evaluation of granules

The granule characterization of the trial batch formulations (A1 to A7) was performed. The results of this study are depicted in tables 8, 9, 10 shows excellent flow properties and compressibility.[9-15] **(Table 2: Pre Compression properties of A1 to A7 batches)**

Formulation and development of hydrophilic matrix tablet

Preparation of Tramadol hydrochloride Matrix Tablets by direct compression method (DC)

Matrix tablets of Tramadol hydrochloride (dose 100 mg) were prepared by direct compression method and wet granulation method. For direct compression (DC), concentrations of gums used were 30 to 70%. All ingredients were sieved through an ASTM #60 sieve (250µm

size), and then weighed quantity of drug was physically mixed with all auxiliary excipients by geometric addition using a glass mortar and pestle for about 10 min. Then magnesium stearate and talc were added as the lubricant/ glidant and thoroughly mixed (zip bag) for 5min. This was the Granules Ready for Compression (GRC). From the GRC, the homogeneous powder mixture for a single matrix was weighed, fed manually into the die of an eight station automatic rotary tablet machine equipped with biconcave die-punch set of 8mm diameter and compressed to a target weight of 100mg and an average hardness of 5–6 kg/cm^2 for all tablets.[1,15,20]

RESULT AND DISCUSSION

Physical characterization of tablet

The hardness, thickness, friability, weight variation and drug content of all the trial formulations (A1 to A7) were determined and the results obtained are mentioned in the tables 2 . The tablets weighing above 250mg have the limit of ± 5% variation according to Pharmacopoeia of India [25]. The tablets evaluated showed the weight variation within limit, and thus passed the test. Weight of tablet is an important factor which affects the drug content of the tablet, if not within the limit. Hardness alone cannot be considered as absolute indicator of the tablet strength. Hence, another parameter measured was the friability of the tablets. The friability of the tablets was found to be less than 1% which was considered within the limit [4]. The measure of these two parameters gives the strength of the tablets during handling, packaging, shipping etc. The drug content of the all the selected matrix formulations were found to be within the limits (98 – 102%) as per Indian Pharmacopoeia.

(Table 3: Post Compression properties of A1 to A7 batches).

Evaluation of Tablets

The tablets were evaluated for different physicochemical parameters such as angle of repose Release profile with burst Zero-order controlled release Burst release Time Cumulative drug released.

Figure 1: Diagram indicating the burst effect phenomenon[10], thickness, bulk density, tap density[11], Carr's index[12], weight variation, thickness, hardness, friability, weight variation[13], drug content, and *in vitro* release. In drug content, 20 tablets of each formulation were weighed and powdered. The quantity of powder equivalent to 100 mg of tramadol HCl was taken and dissolved in 30 mL of distilled water; sufficient amount distilled water was added to produce 50 mL and was filtered. The absorbance was measured spectrophotometrically at 271 nm after suitable dilution.

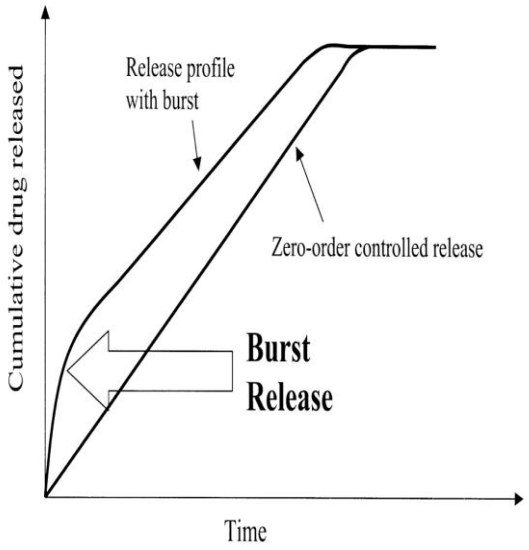

Fig. 1: Diagram indicating the burst effect phenomenon

The *in vitro* dissolution studies were carried out using USP apparatus type II (DA 6D, Veego) at 100 rpm. The dissolution medium consisted of 0.1 N hydrochloric acid for the burst 2 hours and the phosphate buffer pH 6.8 from 3 to 8 hours (900 mL), maintained at 37∘C ± 0.5∘C. The drug release at different time intervals was measured by UV-visible spectrophotometer (Shimadzu 1800) at 271 nm. The release studies were conducted in triplicate (6 tablets in each set) and the mean values were plotted versus time with standard deviation (SD) of less than 3, indicating the reproducibility of the results.

Selection of levels of excipient

As xyloglucan is a natural gum it was used as a release modifying polymer, in trial batch from A1 to A7. When it was used in the range of 50 to 350 mg, it was observed that as the concentration of polymer increased the release retarding effect of the formulation got stronger to the extent that there was incomplete release of drug observed in the formulations A6 and A7 which showed only 70.34 and 66.40 percent drug release at the end of twelfth hour where as formulation A1 showed complete release of drug well before tenth hour (as shown figure 11) indicating inability of the polymer to retard the drug release up to twelfth hour at low concentration i.e. 50 mg. Thus the desirable amount of xyloglucan polymer required to have sustained as well as complete release of drug at the end of twelfth hour was limited in the range 150 to

250 mg per tablet. Additionally there was burst effect seen with the trial batch formulations from A1 to A7 at second hour of dissolution studies where there was a non linear burst release of drug, such effect is commonly observed in formulations using hydrophilic polymers as release retardant .

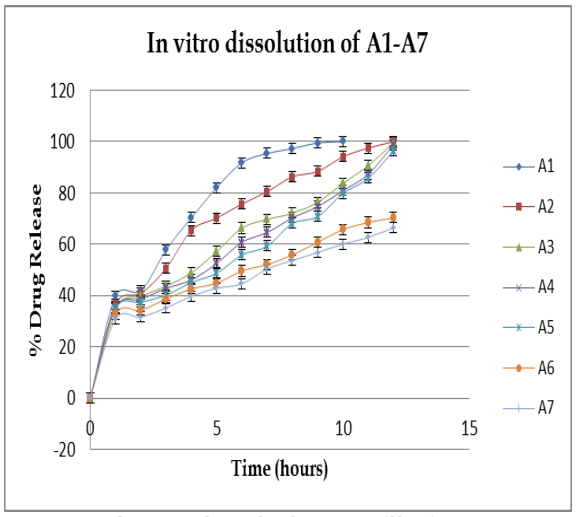

Fig. 2: **Dissolution profile for batches A1 to A7**

The formulations A1 to A7 followed peppas as best fit model, with release exponent (n) > 0.5 indicating non fickian anomalous drug transport mechanism i.e. by dissolution, diffusion and erosion. Also the regression coefficient of all the formulation was near to 0.9989 as shown in thetable 20. The pre and post compression properties of the formulation A1 to A7 are shown in table 23. The granules showed good flow properties and good compressibility. Swelling study result showed slow and gradual increase in swelling index with time, as xyloglucan does not swell instantaneously as soon as it comes in contact with water as shown in figure 3; which results in burst release due to improper swelling. **(Table 4: Dissolution data for formulation from A1 to A7).**

Thus, an additional rate retarding polymer was selected in order to prevent burst effect. A synthetic polymer such as HPMC K100M was selected which is well known for achieving high viscosities instantaneously when in contact with water.The granules showed good flow properties and good compressibility. Swelling study result showed increase in swelling index in the range of 11.4 to 14.5 % within first hour and a range of 21.4 to 25.6 % at the end of twelfth hour, this difference over previous batch (A1 to A7) was due to HPMC K100M which showed immediate swelling as compared to that of xyloglucan; as a result slight control over burst release could be achieved.

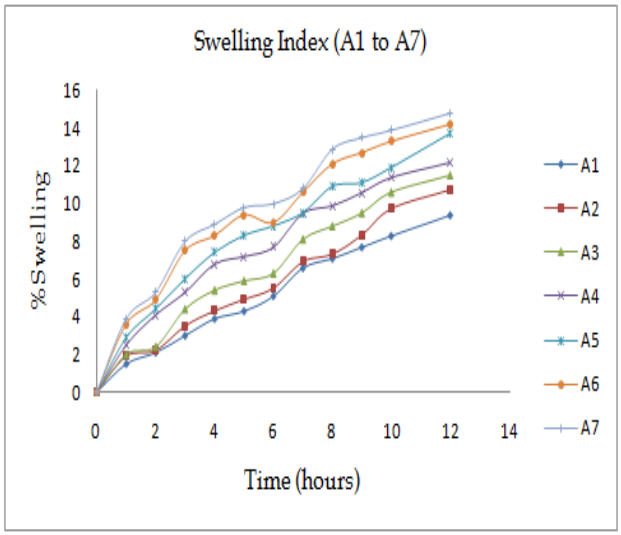

Fig. 3: Swelling index for A1 to A7 formulation

Evaluation of tablets

The prepared hydrophilic matrix tablets (F1 to F7) were evaluated for various parameters. Table 29 gives the results of the evaluation parameters with their standard deviation values.

Physical evaluation

The tablets were within limits of weight variation allowed by I.P. 1996. Hardness of the tablets was within 5.6- 7.1 kg/cm^2 which indicated excellent mechanical strength. Diameter of the tablets was close to 10 mm (9.9-10.1). Thickness varied from 3.83-4.40 mm. The dimensions of the tablets have to be specific, and they should not differ ±5% of the average value. The thickness of the tablets evaluated was found to be within given limits. In physico-chemical evaluation for the design batches (F1 to F7), the pre compression flow properties (ass shown in table 29) such as angle of repose was in range of 25.55° to 29.85 °, carrr's index in rage of 11.17 to 19.86, hausner's ratio in the range of 1.13 to 1.24 indicating good flow properties and post compression properties such as hardness in the range of 5.5 to 7.4 kg/cm^2 , friability in the range of 0.34 to 0.74 indicates efficient method of preparation. (**Table 4**: **Post compression properties of optimization batches F1-F7)**

Weight variation

The tablets weighing above 250mg have the limit of ±5% variation according to Indian Pharmacopoeia. The tablets evaluated showed the weight variation within limit, and

thus passes the test. Weight is an important factor which affects the drug content of the tablet, if not within the limit.

Friability

The friability of the tablets was found to be less than 1% which was considered within the limit [50]. The measure of these two parameters gives the strength of the tablets during handling, packaging, shipping etc.

Drug content of the tablets

The uniformity in drug content is an important measure. It gives the percentage of drug present per unit dosage form. The value of drug content evaluated ranged from 98.10 to 101.31%. Hence, the tablets prepared showed good content uniformity.

Dissolution test

The rate of drug absorption for many drug moieties in the gastrointestinal track is often determined by the rate of drug dissolution from the tablet. The rate of drug dissolution may be directly related to the efficacy of the tablet product, as well as the bioavailability differences between the formulations. Therefore, an evaluation as to whether or not a tablet releases its drug contents when placed in the environment of the gastrointestinal track is often a fundamental concern to the tablet formulator. This test of dissolution is most of the times useful to specific types of dosage forms such as; control release, sustain release, time dependent, targeted etc. to know the approximate drug release behavior of dosage form in the GIT[13].

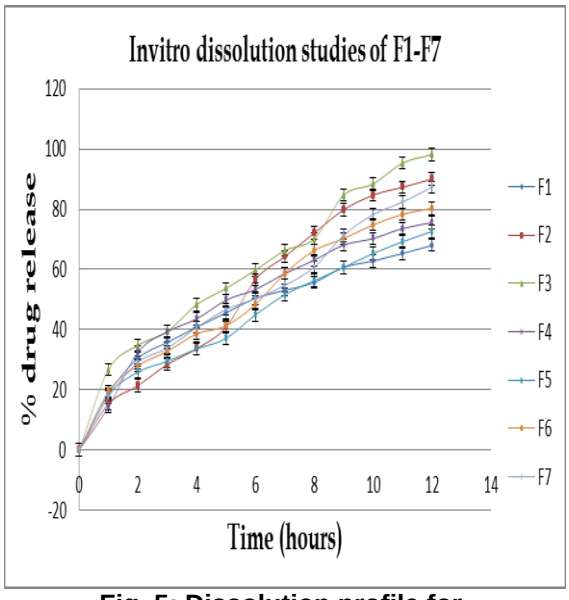

Fig. 5: Dissolution profile for optimization batches from F1-F7

Figure 5 depicts the rel_2 Hr and rel_{12} Hr respectively for all 7 batches (F1-F7) showed a wide variation. Form the dissolution study of seven batches, percent release of drug at second hour (rel_2Hr) was found to be in range of 15.21% to 33.74 % and percent release of drug at twelfth hour (rel_{12} Hr) was found to be in range of 88.79% to 99.46%. All the batches from F1 to F7 followed Higuchi kinetics (as shown in table 5). **(Table 5**: **Dissolution model for F1 to F7 formulation)**

Preliminary Trials

In trial batches from *A*1 to *A*7CMxyloglucan was used in the range of 50 to 250 mg; it displayed a retardation of drug release commensurate to theconcentration of polymer. For the comparison of native xyloglucan and derivative carboxymethyl xyloglucan, trial batches F1 and F7each containing 150 mg polymer were prepared . Batch F1 containing plain xyloglucan sustained-release only for 4hours while batch F7containing CM-xyloglucan sustained release up to 7 hours .The percentage drug release at second hour for F1 to F7formulations was in the range of 87.90% to 53.39%, respectively, as shown in Figure 3, while only F3 to F5formulations were able to retard drug release up to 7 to 8 hours. It was found from the initial trials that 150 to 250 mg offormulations were able to retard drug release up to 7 to 8 hours. But at 150 mg concentrationrelease was sustained up to 7 hours so that minimum level should be slightly more than 150 mg, while for 200 and 250 mg concentration release was almost similar, hence, 200 mg was decided as a higher level of the polymer. The granule characterization of the trial batch formulations(F1 to F7) was performed. The results of this study are depicted in Table 2 which shows excellent Flow properties and compressibility.

Swelling Study

Swelling study results showed slow and gradual increase in swelling index with time and concentration of CM-xyloglucan, as CM-xyloglucan does not swell instantaneously as soon as it comes in contact with water as shown in Figure 4; this results in burst release due to improper swelling. Therefore, to avoid the burst release effect, we have added HPMC K100 in the small quantity. Swelling of F 7batch is highest because it contains a higher amount of polymer. If swelling is more then it increases the path length required for water to travel inside the core of tablet, which gives more sustained-release.

CONCLUSION

Sustained drug release following matrix kinetics attained in the current study indicates that the hydrophilic matrix tablet prepared using carboxymethyl xyloglucan and HPMC-K-100M can successfully be employed sustain the drug release up to 8 to 12 hours as shown in Table 5. Carboxymethyl xyloglucan played major role in sustaining release of tramadol at later stage of release profile, whereas HPMC-K- 100M prevented the burst effect by controlling the sudden release of drug from the dosage form at the initial stage of the release profile. It was concluded that appropriate balancing between various levels of the polymers may contribute better results.

Table 1: Composition of F1 to F7 formulation

Ingredients	F1	F2	F3	F4	F5	F6	F7
Tramadol HCL	100	100	100	100	100	100	100
TSP	200	180	180	190	190	180	186.67
HPMC	10	30	10	20	10	20	16.67
DCP	30	50	30	40	40	40	36.67
Talc	5	5	5	5	5	5	5
Magnesium Stearate	5	5	5	5	5	5	5
PVP K-30	30	30	30	30	30	30	30
Isopropyl alcohol	q.s	q.s	q.s	q.s	q.s	q.s	q.s

All quantities are in mg

Table 2: Pre Compression properties of A1 to A7 batches

Parameters	A1	A2	A3	A4	A5	A6	A7
Bulk density	0.506 ± 0 .02	0.493 ± 0.03	0.512 ± 0.04	0.283 ± 0.03	0.306 ± 0.04	0.304 ± 0.03	0.289 ± 0.03
Tapped density	0.582 ± 0.04	0.555 ± 0.03	0.581 ± 0.02	0.325 ± 0.06	0.352 ± 0.02	0.349 ± 0.04	0.335 ± 0.04
Angle repose	19.24± 0.15	21.91± 0.12	19.86± 0.08	23.05± 0.19	20.18 ±0.04	22.61 ±0.17	21.62 ±0.11
Carrs index	13.08 ± 0.02	11.25 ± 0.03	11.82 ± 0.03	12.95 ± 0.03	13.08 ± 0.03	12.92 ± 0.02	13.75 ± 0.02
Hausners ratio	1.15 ± 0.16	1.12 ± 0.09	1.13 ± 0.09	1.14 ± 0.02	1.15 ± 0.06	1.14 ± 0.06	1.16 ± 0.022

Table 3: Post Compression properties of A1 to A7 batches

Parameters	A1	A2	A3	A4	A5	A6	A7
Hardness	6.4 ± 0.16	7.5 ± 0.14	5.70 ± 0.22	5.50 ± 0.91	5.4 ± 0.08	6.8 ±0.17	5.6 ± 0.05
Friability	0.34 ± 0.22	0.31 ± 0.12	0.28 ± 0.31	0.35 ± 0.18	0.29± 0.27	0.28 ± 0.52	0.33 ± 0.71
Weight variation	208 ± 1.03	261 ± 0.83	308 ± 1.09	358 ± 0.95	409 ± 0.83	459 ± 1.16	511 ± 1.40
Drug content	98.34 ± 0.22	99.21 ± 0.11	100.56 ± 0.89	98.10 ± 0.18	95.31 ± 0.21	97.11 ± 0.12	98.15 ± 0.28
Thickness (mm)	3.154 ± 0.009	3.115 ± 0.009	2.89 ± 0.015	3.133 ± 0.014	3.03 ± 0.036	3.06 ± 0.02	3.92 ± 0.018

Table 4: Dissolution data for formulation from A1 to A7

Batch code	Release exponent (*n*)	Kinetic constant (*K*)	Regression coefficient (R)	Best fit model
A1	0.6948	32.71	0.9692	Peppas
A2	0.7634	28.67	0.9736	Peppas
A3	0.7791	25.36	0.9795	Peppas
A4	0.8372	19.82	0.9817	Peppas
A5	0.6834	15.26	0.9854	Peppas
A6	0.7498	9.07	0.9893	Peppas
A7	0.6542	-0.18	0.9986	Peppas

Table 5: **Post compression properties of optimization batches F1-F7**

Parameters	F1	F2	F3	F4	F5	F6	F7
Hardness (kg/cm^2)	6.2 ± 0.33	6.1 ± 0.26	6.1 ± 0.18	6.4 ± 0.34	6.4 ± 0.17	6.1 ± 0.32	6.4 ± 0.13
Friability	0.74 ± 0.21	0.58 ± 0.11	0.41 ± 0.22	0.70 ± 0.16	0.52 ± 0.12	0.67 ± 0.23	0.34 ± 0.22
Uniformity of weight (mg)	200.9 ± 0.34	200.78 ± 0.45	200.98 ± 0.55	200.19 ± 0.36	200.43 ± 0.12	200.5 ± 0.24	200.78 ± 0.13
Drug content (%)	98.34 ± 0.22	99.21 ± 0.11	98.10 ± 0.18	98.20 ± 0.39	98.7 ± 0.21	98.55 ± 0.67	98.56 ± 0.89

± SD (standard deviation), n=3

Table 6: **Dissolution model for F1 to F7 formulation**

Batch code	Release exponent (*n*)	Kinetic constant (*K*)	Regression coefficient (R)	Best fit model
F1	0.6142	9.49	0.9986	Higuchi
F2	0.6017	5.64	0.9795	Higuchi
F3	0.7181	4.02	0.9736	Higuchi
F4	0.6698	0.89	0.9905	Higuchi
F5	0.6510	-0.18	0.9893	Higuchi
F6	0.5814	-0.19	0.9854	Higuchi
F7	0.5619	-0.29	0.9957	Higuchi

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