

Formulation and Evaluation of Fast Dissolving Tablets of Diclofenac Sodium by Novel Hole Technology

Renati Damodar^{1*}, Babji Movva¹, Mallikarjun PN¹, Chaitanya Pasumarthy², Nishanth Kona³ and Varsha PV⁴

¹Department of Pharmaceutics, Vignan Institute of Pharmaceutical Technology, Visakhapatnam, Andhra Pradesh, India

²Mother Teresa College of Pharmacy, Ghatkesar, Hyderabad, India

³Department of Pharmaceutics, Sree Siddaganga College Pharmacy, Tumkur, Karnataka, India

⁴Department of Biotechnology, GITAM University, Visakhapatnam, Andhra Pradesh, India

Abstract

Research has done to prepare Diclofenac Sodium quick dissolving tablets by Hole technology. Once these quick dissolving tablets contact with gastro enteric fluids, the fluid can enter the hole within the tablet and immediate breaking of the tablet goes to take place. This quick disintegration of tablets is additionally influenced by the formation of latest absolute space. The ready FDTs were subjected to numerous pre and post formulation studies. Its disintegration and dissolution rates were compared with the management formulation (without hole). *In-vitro* drug release of FDTs (DH6) showed virtually 100.92% of the drug was discharged at sixth minute, whereas the management formulation D12 shows the 99% drug release at 20th minute. Overall, this method is novel and most helpful for formulation into quick dissolving tablets.

Keywords: Hole technology; Diclofenac sodium; Novel fast dissolving tablets; Hole formation

Introduction

The oral drug delivery has been celebrated for many years because the most generally used route of administration among all the routes that have been explored for the general delivery of drugs via varied pharmaceutical product of different indefinite quantity forms [1]. The explanations that the oral route achieved such popularity could also be partly attributed to its simple administration still because the ancient belief that by oral administration the drug is still absorbed because the foodstuffs that are ingested daily [2]. Pharmaceutical product designed for oral delivery and presently available on the prescription and over-the-counter markets are largely the immediate-release sort, that are designed for immediate unreleased drug for speedy absorption. These fast-dissolving tablets ensure complete solubilization of tablet through surface erosion, leading to elimination of lag time for disintegration thereby offering quicker absorption and speedy onset of action [1-3].

Despite increasing interest in controlled- unreleased drug delivery systems, the most common tablets are those supposed to be enclosed whole and to disintegrate and unreleased their medicaments quickly within the gastro enteral tract. In additional recent years, increasing attention has been paid to formulating not solely fast dissolving and / or disintegrating tablets that are enclosed, but conjointly orally disintegrating tablets that are indented to dissolve and/or disintegrate quickly within the mouth [4-6].

Fast dissolving tablets (FDTs) are solid single-unit dosage forms that are place in the mouth, allowed to disperse/dissolve in the saliva and then swallowed without the need for water. FDTs are appreciated by a significant segment of the population, particularly children and elderly who have difficulty in swallowing conventional tablets or capsules. The most desirable formulation for use by the elderly is one that is easy to swallow and easy to handle. Since such a tablet can disintegrate in only a small amount of water in the oral cavity, it is easy to take for any age patient, regardless of time or place. For example, it can be taken anywhere at any time by anyone who do not have easy access to water. It is also easy to dose the aged, bed-ridden patients, or infants who have problems swallowing tablets and capsules. Recently, many companies have researched and developed various different types

of fast-dissolving tablets by adopting different techniques. However, some of these technologies have disadvantages. New equipment, such as freeze-driers and specially molded tableting machines, were required for their production. Furthermore, these formulations were difficult for the aged to handle because of inadequate strength [7-12].

The Diclofenac sodium is a non steroidal anti inflammatory drug. It comprise a large family of weak acidic drugs whose pharmacological effects result primarily from the inhibition of cyclooxygenase (COX) an enzyme that catalyses the first step in the synthesis of prostaglandins from arachidonic acid and other precursor fatty acids. Since its solubility is very high in upper G.I. and need of fast releasing action in case of acute pain it is formulated as fast dissolving tablet [13-18].

Therefore the objectives of present research investigation were to formulate fast-dissolving tablets with sufficient hardness for handling and be manufactured by commonly used production methods and equipment.

Materials and Methods

Materials

Diclofenac Sodium was obtained as a gift sample from Hetero drugs limited Laboratories, Hyderabad, India. Sodium starch glycolate, cross carmellose sodium, mannitol, sodium saccharine were procured from Yarrow Chem. Products, Mumbai, camphor was procured from Saptagir camphor limited, Anantapur. Potassium dihydrogen phosphate, methanol Reagent was procured from Merck limited,

***Corresponding author:** Renati Damodar, Department of Pharmaceutics, Vignan Institute of Pharmaceutical Technology, Visakhapatnam, Andhra Pradesh, India, Tel: +918500932050; E-mail: renatidamodar@gmail.com

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Mumbai. Lactose, magnesium stearate and talc I.P were procured from Molychem, Mumbai, India. All other chemicals were of analytical grade.

Preparation of FDTs by novel hole technology

All the ingredients in Table 1 were accurately, 100mg camphor tablets were prepared by taking plain camphor granules and compressed into tablets.

Diclofenac sodium, super disintegrants and exponents were mixed in a container. Talc and Magnesium stearate after passing through sieve # 60 mixed and blended with initial mixer in the container. This mixture is then placed in the die cavity and at the centre of the die cavity, previously compressed camphor tablets were kept then compressed into tablets. These tablets containing tablet in tablet. i.e. Camphor tablet is present in Diclofenac tablet. After compression, these tablets were dried at 60°C by keeping the tablets in a hot air oven until complete removal of camphor to make tablets with hole at the center leading to formation of extra absolute surface area (Figure 1).

Evaluation of Tablets

Pre compression parameters

Characteristics like tapped density, bulk density, carr's index, hausner,s ratio were studied for powder blend of formulations which are ready to compress in to tablets [19-35].

Post compression parameters

All the prepared tablets were subjected to various physical characteristics like Crushing strength, Friability, Thickness, Diameter, Hole depth, Disintegration time, Wetting time, Weight variation, Drug content (Table 3).

Weight variation test

Weight variation test was done by weighing 20 tablets individually, by using electronic balance. Calculating the average weight and comparing the individual tablet weight to the average weight [21-23].

Tablet thickness

The thickness was measured by placing tablet between two arms of the Vernier calipers. 5 tablets were taken and their thickness was measured.

S. No.	Ingredient (mg/tab)	DH1	DH2	DH 3	DH 4	DH 5	DH 6
1	Diclofenac Na	75 mg	75 mg	75 mg	75 mg	75 mg	75 mg
2	Cross carmellose Sodium	10 mg	20 mg	30 mg	-	-	-
3	Sodium Starch Glycolate	-	-	-	10 mg	20 mg	30 mg
4	Lactose	175 mg	175 mg	175 mg	175 mg	175 mg	175 mg
5	Mannitol	230 mg	220 mg	210 mg	230 mg	220 mg	210 mg
6	Sodium saccharine	6 mg	6 mg	6 mg	6 mg	6 mg	6 mg
7	Magnesium stearte	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg
8	Talc	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg
9	Camphor	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg
	Total weight after sublimation	500 mg	500 mg	500 mg	500 mg	500 mg	500 mg

Table 1: Formulation chart of Diclofenac Sodium FDT with Hole technology.

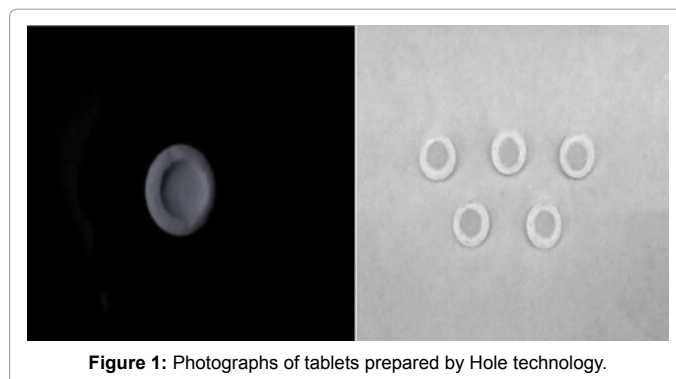


Figure 1: Photographs of tablets prepared by Hole technology.

Tablet hardness

The tablet hardness, which is the force required to break a tablet in a diametric compression force. The hardness tester used in the study was Monsanto hardness tester, which applies force to the tablet diametrically with the help of an inbuilt spring.

Tablet friability

The friability of the tablets was measured in a Roche friabilator (M/s. Elite Scientific & Equipments.). Tablets of a known weight (W_0) or a sample of 20 tablets are dedusted in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1%. Determination was made in triplicate.

$$\% \text{ Friability} = 100 (W_0 - W) / W_0$$

In vitro characterization of prepared tablets

In vitro disintegration time

In the disintegration time study, the tablets were taken and introduced in each tube of disintegration apparatus, and the tablet rack of the disintegration apparatus was positioned into a 1-litre beaker containing 900ml of distilled water and time of disintegration was recorded at $37 \pm 2^\circ\text{C}$ [23-28].

In the wetting time study

In wetting time study a piece of tissue paper folded twice was placed in a petridish (with internal diameter 6.5 cm) containing 5 ml of distilled water. A tablet was placed on the paper and the time for complete wetting of the tablet was measured in seconds [36-42].

Drug content analysis

Total 10tablets were weighed and powdered. The powder equivalent to Diclofenac Sodium was taken and dissolved in 0.1N HCl. After that an aliquot of the filtrate was diluted and analyzed spectrophotometrically (Elite UV- 150 double beam spectrophotometer.) at 314 nm [43,44].

In vitro release studies

The *in vitro* dissolution study was carried out in the USP dissolution test apparatus (M/s Lab India (Model – DS 8000) type 2 (paddle). 900 ml of the dissolution medium (Phosphate buffer pH 6.8) was taken in vessel and the temperature was maintained at $37 \pm 0.5^\circ\text{C}$. The speed of the paddle was set at 50 rpm. 5ml of the dissolution medium was withdrawn and the same amount of fresh medium was replenished to the dissolution medium. The sample withdrawn was filtered and

diluted with Phosphate buffer pH 6.8 prior to analysis in the UV Spectrophotometer (Elite UV- 150 double beam spectrophotometer) at 285 nm [45-47].

Results and Discussion

Compatibility studies

Infrared spectroscopic study: Fourier transformed (FTIR) spectrum of Diclofenac, Drug with different excipients were obtained on a FTIR (Perkin-Elmer) using the KBr disk method. The prominent IR absorption peaks of Diclofenac showed at 3381.57 cm^{-1} due to NH stretching of secondary amine. Peak at 1572.66 cm^{-1} due to -C=O stretching of carboxyl ion. Peak at 745.35 cm^{-1} because of c-cl stretching. All these principal IR peaks of Diclofenac Sodium were present in all formulations. This clearly indicates that there is no interaction between drug and carrier.

Pre compression parameters

The Bulk density of all the formulations were within the range of 0.51 ± 0.005 to $0.56 \pm 0.005\text{ g/ml}$ and Tapped density was found to be in the range of 0.61 ± 0.03 to $0.66 \pm 0.03\text{ g/ml}$ (good flow property). The Angle of repose of powder blends of all formulation was found to be in the range of 19.21 ± 0.12 to $29.62^\circ \pm 0.2$ (good flow property). The calculated Carrs index of all formulations was found to within the range of 13.84 ± 0.15 to $17.74\% \pm 0.16$ (good flow property). The calculated Hausners ratio of all the formulations was found to be in the range of 1.162 ± 0.13 to 1.21 ± 0.03 (good flow property). The values of pre-compressional parameters evaluated were within the prescribed limits and indicated good free flowing properties.

Post compression parameters

The post compression parameters of all batches were studied and shown in Table 2. The crushing strength of tablets prepared by hole technology were within the range of 3.5 ± 0.25 to $3.5 \pm 0.5\text{ kg/cm}^2$. The loss of percentage of weight in friability was found to be 0.39 ± 0.08 to 0.53 ± 0.06 which is less than 1% which indicates tablets has good mechanical resistance. The thickness and diameter of prepared tablets was found to in the range of 3.812 ± 0.02 to $4.0 \pm 0.03\text{ mm}$ and 12.80 ± 0.05 to $12.90 \pm 0.04\text{ mm}$ respectively. The hole depth of all formulations prepared by hole technology was found to be in the range of 1.66 ± 0.22 to $1.75 \pm 0.04\text{ mm}$. The wetting time of all formulations prepared by hole technology was found to be in the range of 21 ± 0.49 to $44 \pm 0.61\text{ sec}$. The disintegration time of all formulations prepared by hole technology was found to be in the range of 14 ± 0.53 to $33 \pm 0.65\text{ sec}$ and was shown in Table 4. The weight variation of all formulations prepared by hole technology was found to be in the range of 497.5 ± 0.19 to $498.5 \pm 0.18\text{ mg}$. The drug content of all formulations prepared

by hole technology was found to be in the range of 98.9 ± 1 to $101.5 \pm 1.25\%$.

In vitro dissolution studies

The *in vitro* dissolution study was carried out in the USP dissolution test apparatus (M/s Lab India (Model – DS 8000) type 2 (paddle). 900 ml of the dissolution medium (Phosphate buffer pH 6.8) was taken in vessel and the temperature was maintained at $37 \pm 0.5^\circ\text{C}$. The results were shown in Table 4. The cumulative% of drug release of formulations prepared by hole technology was found to be, DH1 showed 100% drug released at 12 min. DH2 showed 98.35% drug released at 10 min, DH3 showed 100.92% drug released at 10 min, DH4 showed 97.71% drug released at 10 min, DH5 showed 96.42% drug released at 8 min, DH6 showed 100.92% drug released at 6 min. The cumulative% of drug release of formulations prepared by direct compression was found to be, D7 showed 100.28% drug released at 50 min, D8 showed 96.42% drug released at 40 min, D9 showed 100.8% drug released at 25 min, D10 showed 99.64% drug released at 45 min, D11 showed 100.9% drug released at 45 min, D12 showed 98.35% drug released at 20 min.

The T50 and T90 were calculated for all formulations and were shown in Time for 50% of dissolution was found to in the range of 3min 30 sec to 5 min 36 sec for formulations with hole technology. Time for 50% of dissolution was found to in the range of 3 min 30 sec to 6 min for formulations with direct compression. Time for 90% of dissolution was found to in the range of 5 min 36 sec to 10 min for formulations with hole technology. Time for 90% of dissolution was found to in the range of 17 min to 40 min for formulations with direct compression. From the results DH6 was selected as best formulation since it showed total drug release in 6 minutes.

Stability studies of optimized formulation

Optimized formulation was exposed for accelerated conditions as per ICH guidelines. ($40^\circ\text{C} / 75\% \text{ RH}$ for a period of 3 months. Tablets were evaluated for physicochemical properties, drug release. The Stability studies on optimized formulation of Diclofenac Sodium fast dissolving tablets were conducted according to the ICH guidelines. The various parameters tested during studies of Diclofenac Sodium fast dissolving tablets the formulation were withdrawn at suitable intervals (initial and 1 month) and analyzed visually for physical appearance and evaluated for different tests. The tablets showed no visual differences and compiled with description. The percentage of drug release from the formulation DH6 at different intervals of time is given in Table 5 and was found to be matching with specification. The results were shown in Table 5. From the results, it can be concluded that the formulation DH6 of Diclofenac fast dissolving tablets was stable at accelerated conditions of temperature and humidity.

Parameter	Formulations					
	DH1	DH2	DH3	DH4	DH5	DH6
Hardness (kg/cm) \pm SD, n=3	3.5 ± 0.25	3 ± 0.5	3.5 ± 0.25	3.5 ± 0.25	3 ± 0.5	3.5 ± 0.25
Friability (% w/w) \pm SD, n=3	0.52 ± 0.07	0.50 ± 0.08	0.48 ± 0.07	0.53 ± 0.06	0.49 ± 0.08	0.52 ± 0.07
Thickness (mm) \pm SD, n=6	3.86 ± 0.03	3.9 ± 0.02	4.0 ± 0.03	3.96 ± 0.03	3.89 ± 0.03	3.95 ± 0.02
Diameter (mm) \pm SD, n=6	12.84 ± 0.08	12.82 ± 0.06	12.81 ± 0.06	12.80 ± 0.05	12.84 ± 0.05	12.83 ± 0.06
Wetting time(Sec) \pm SD, n=6	30 ± 0.54	25 ± 0.71	21 ± 0.49	44 ± 0.61	39 ± 0.52	33 ± 0.49
Weight variation (mg) \pm SD, n=10	498.5 ± 0.18	497.80 ± 0.14	497.5 ± 0.19	498.2 ± 0.17	497.50 ± 0.18	498.3 ± 0.16
In vitro disintegration time (Sec) \pm SD, n=6	20 ± 0.79	17 ± 0.65	14 ± 0.53	33 ± 0.65	29 ± 0.51	25 ± 0.63
Drug content (%) \pm SD, n=6	100.50 ± 1.00	101.50 ± 1.25	99.8 ± 1.25	98.9 ± 1.00	100.50 ± 1	101.5 ± 1.25
Hole depth(mm)	1.66 ± 0.02	1.75 ± 0.04	1.68 ± 0.02	1.72 ± 0.04	1.68 ± 0.03	1.72 ± 0.04

Table 2: Physical characteristics of tablets.

Formulation	disintegration time (sec)	Wetting time (sec)
DH1	20 sec	30 sec
DH2	17 sec	25 sec
DH3	14 sec	21 sec
DH4	33 sec	44 sec
DH5	29 sec	39 sec
DH6	25 sec	33 sec

Table 3: Disintegration and wetting time.

Time in min	DH1	DH2	DH3	DH4	DH5	DH6
0	0	0	0	0	0	0
2	16.07	23.14	27.64	23.78	28.28	30.21
4	35.35	48.85	57.21	48.85	58.5	62.35
6	53.35	83.57	90	86.14	92.57	100.92
8	83.57	91.28	99.64	88.07	96.42	-
10	89.35	98.35	100.92	97.71	-	-
12	100.28	-	-	-	-	-

Table 4: Dissolution studies of formulations.

S No	Test	Initial	40°C/75 %RH After 3 months
1	Thickness (mm) ± SD	3.95 ± 0.25	3.85 ± 0.0057
2	Hardness (kg/cm ²) ± SD	3.5 ± 0.25	3 ± 0.011
3	Friability (% W/W) ± SD	0.52 ± 0.07	0.89 ± 0.002
4	Weight variation (%) ± SD	498.3 ± 0.16	485 ± 0.577
5	Drug content (%) ± SD	101.5 ± 1.25	97.2 ± 0.115
6	Wetting time (sec)	33 sec ± 0.49	30 sec ± 0.5
7	Disintegration time (sec)	25 sec ± 0.63	21sec ± 0.39
8	Drug release	100% at 6min	97% at 6min

Table 5: Results for stability studies.

Drug release kinetics

The drug release profiles of the tablets were studied includes zero order (Figure 2), First order (Figure 3), Higuchi square root of time model (Figure 4), Hixon- Crowell model (Figure 5 and Korsmeyer-peppas model (Figure 6). From the results it is implying that the release kinetics from the FDT tablet follows zero order kinetics. Especially batch DH6 showed R² value of 0.9948 indicating the drug release followed zero order kinetics. The R² values of all formulations were showed in Table 6.

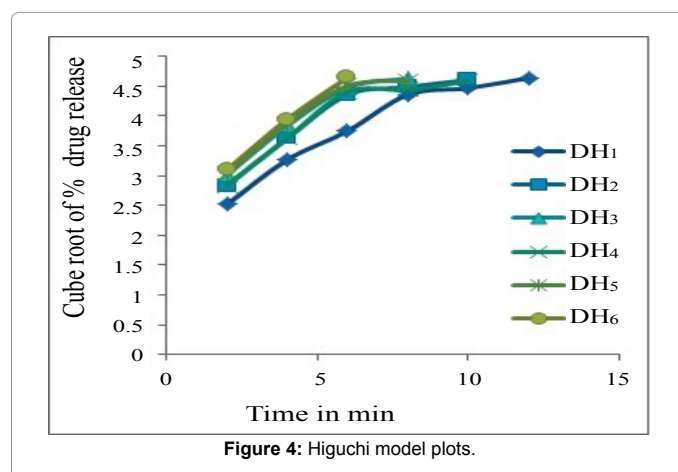


Figure 4: Higuchi model plots.

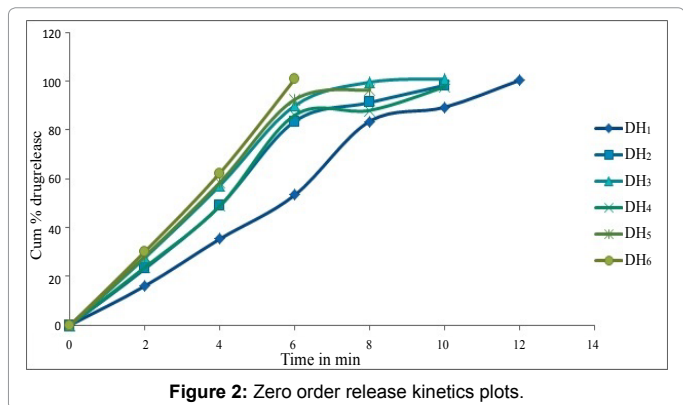


Figure 2: Zero order release kinetics plots.

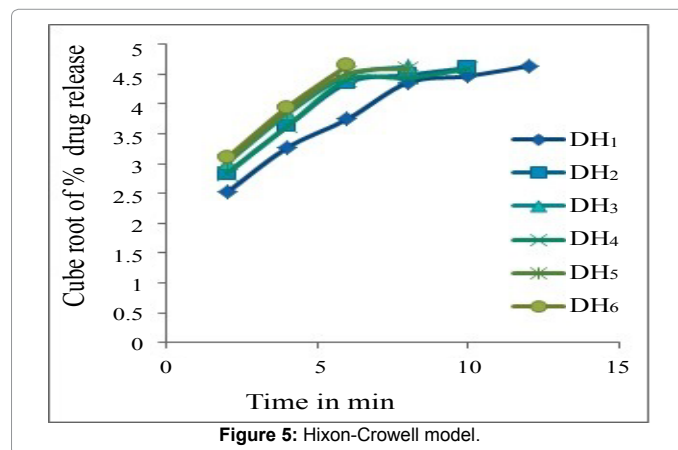


Figure 5: Hixon-Crowell model.

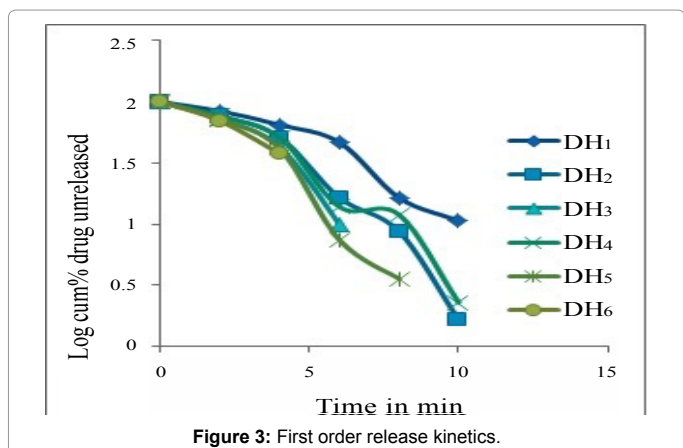


Figure 3: First order release kinetics.

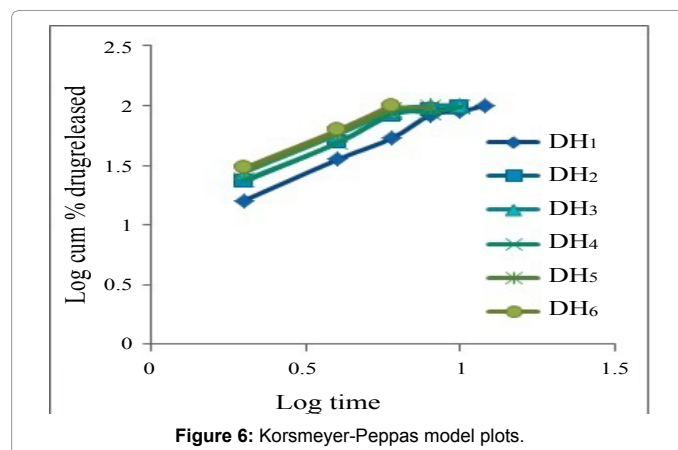


Figure 6: Korsmeyer-Peppas model plots.

Formulation	Zero order	First order	Higuchi plots	Hixonand crowell	Korsemeyerpeppas plots
DH1	0.9783	0.920	0.9777	0.9263	0.8944
DH2	0.9479	0.9293	0.9554	0.8708	0.8505
DH3	0.9255	0.8242	0.936	0.9274	0.8249
DH4	0.9353	0.9249	0.9366	0.848	0.843
DH5	0.9612	0.9342	0.9568	0.9037	0.842
DH6	0.9968	0.9774	0.9835	0.994	0.8624

Table 6: Drug release kinetics (R^2 values of formulations).

Conclusion

The tablets prepared with hole technology showed all the parameters like hardness, friability, weight variation within the limits. All the formulations with increased concentrations of super disintegrants showed better drug release compared to the formulations with less concentration of super disintegrants. The formulation DH6 with 30 mg of SSG showed disintegration in 25 sec and a wetting time of 33 sec and showed total drug release in 6 min. The formulation is effectively useful in treatment of acute pains.

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