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FORMULATION AND EVALUATION OF FLURBIPROFEN TABLET BY NOVEL HOLE TECHNOLOGY

Upadhyay N and Dr. Agrawal S.

Department of Pharmaceutics, Swami Vivekananda College of Pharmacy, Indore-452020 Madhya Pradesh, India

ABSTRACT

The objective of the present study was to develop flurbiprofen quick dissolving tablets by Hole technology. Once these Fast dissolving tablets contact with gastric fluids, the fluid enters the hole formed within the tablet and result in immediate breaking of the Tablet. This quick disintegration of tablets is additionally influenced by the formation of latest absolute space. The ready FDTs was subjected to numerous pre and post formulation studies. Its dissolution and disintegration rate was compared with the formulation (without hole). In-vitro drug release of FDTs F5 showed virtually 98.92% of the drug was in fourteen minute, whereas the formulation F1 showed the 97.07% drug release in seventeen minute. Overall, this method is novel and most helpful for formulation into quick dissolving tablet.

Keywords: Hole technology; Flurbiprofen; Novel fast dissolving tablet; Hole formation.

INTRODUCTION

FDDTs dissolves or more commonly disintegrate rapidly in the saliva without the aid of water and should have pleasant mouth feel. Convenience of administration while travelling where they may not be an accesses to water. Well established in the management of pain, inflammation etc.Easy of portability. Alternative to liquid dosage from. Flurbiprofen is a NSAIDs (Nonsteroidal anti-inflammatory drug) analgesic and antipyretic drug. Because of the limited aqueous solubility it exhibits poor dissolution characteristic and its oral absorption is dissolution rate limited. Therefore, in the present study an attempt has been made to increase its solubility and formulation into rapid disintegrating tablet using various superdisintergrantes. The slightly soluble drug needs modification to make it water soluble. Among different approaches using one of the important approach. Hole technology is the most common approach used and it has been shown to improve pharmaceutical properties like-Solubility, Dissolution, Bioavailability, Stability, Even palatability without affecting their intrinsic lipophilicity or pharmacological.

The reason for selection of flurbiprofen for the formulation of RDT because flurbiprofen is an effective non-steroidal anti-inflammatory drug used for the treatment of rheumatoid arthritis and osteoarthritis.

This method is novel and most helpful for formulation into Fast dissolving tablets. Some of other tablet like diclofenac sodium and etc. was prepared by novel hole technology showed better drug release compared to the formulation with less concentration of super disintegrants.

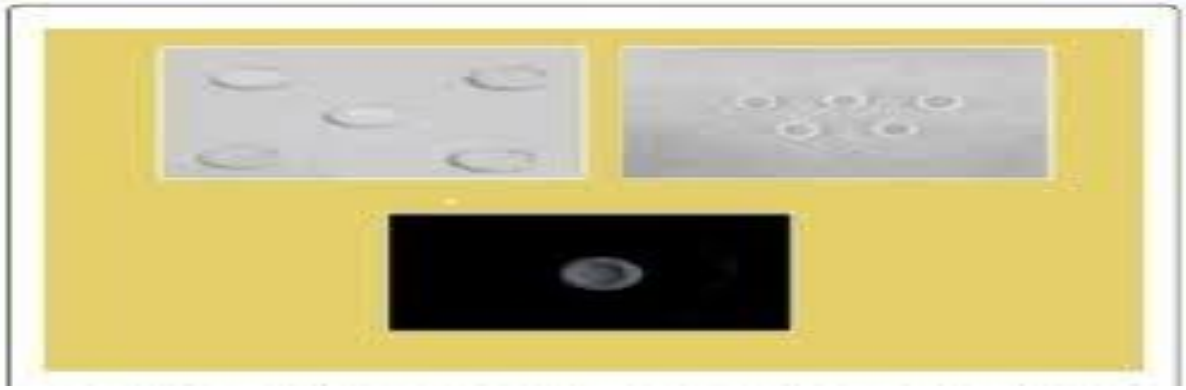

Figure 1. Fast dissolving tablet ready to by Novel Hole Technology

MATERIALS

Flurbiprofen was obtained as gift sample from sun pharma, Hyderabad, India. Sodium corboxy methyl cellulose, Sodium – starch glycollate Lactose SD fine chem. Ltd.,pune,India. Mannitol, Sodium-Saccharine CDH Fine chemicals ltd, Mumbai. All other chemicals were of analytical grade.

Preformulation studies

UV/ visible spectrophotometer method:

The identification of flurbiprofen done by UV spectrophotometer method. The small amount of drug dissolveI an Chloroform and scanned sepctrophotometerically. The spectral data from this scan was used for the preparation of calibration curve of flurbiprofen the scanned spectrum of flurbiprofen is shown in Fig.no. 1, 2

Melting point determination

Melting point determination of flurbiprofen was done by using melting point apparatus. The result is shown in Table no.5

IR spectra

The IR Spectra were recorded using FTIR (Shimadzu Company). The IR spectrum of pure flurbiprofen was interpreted and compared with standard. The IR spectrum is shown in Fig. 3

Qualitative solubility

Qualitative solubility analysis for flurbiprofen was done by dissolving 5 mg. Of drug in 5 ml of solvent. Different solvent were used for the solubility determination in different solvent like water, Ethanol, Octanol, Ether, phosphate buffer (pH7.4), $CHCI_3$ To determine the solubility of drug. The qualitative solubility of flurbiprofen is shown in Table.6

Quantitative solubility

Quantitative solubility analysis for flurbiprofen was done by taking 2ml. Solvent and drug into the solvent until the saturation of solvent with drug. Different solvent ware used for the solubility determine like water, Acetone, Methanol, phosphate buffer (pH 7.4), Chloroform and Ethanol. The conc. Of drug was measured by UV Spectrophotometric technique. The quantitative solubility of flurbiprofen is shown inTtable.7

Partition coefficient

Partition coefficient determination of flurbiprofen was done by simple shaking flask method. The result is shown in Tab.no.5

$$\mathbf{P_{O/W}} = C_{oil} / C_{water}$$

pH determination

pH was determined by pH meter. The result is shown in Tab.no.5

Formulation method

One hundred mg camphor tablet was prepare by taking plain camphor granules and compressed into tablets. Flurbiprofen and super disintegrants was 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 center of the die cavity, previously compressed camphor tablet was kept then compressed into tablets. These tablets containing tablet in tablet. That is camphor tablet is present in flurbiprofen tablet. After compression, these tablet were dried at 60^0C by keeping the tablet in a hot air oven until complete removal of camphor to make tablet with hole at the center leading to formulation of extra absolute surface area.

Excipients for use in formulation superdisintergrants like sodium carboxymethylcellulose and sodium starch glycollate. Sodium saccharin as a sweetening agent, Magnesium stearate as a lubricant, Mannitol as a Vehicle and Bulking agent, Lactose as a diluent & binding agent, Talc as a glident.

Formulation table

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Flurbiprofen	100	100	100	100	100	100
SCMC	20mg	10	30	-	-	-
SSG	10	-	-	20	30	20
L	175	175	175	150	140	175
M	185	205	185	220	220	195
SC	6	6	6	6	6	6
MS	2	2	2	2	2	2
Talc	2	2	2	2	2	2
Camphor	100	100	100	100	100	100

Table 4. Composition of rapid disintegration tablet of flurbiprofen

SCMC Sodium corboxy methyl celluloses -Sodium starch glycollate, L-Lactose, M-Mannitol.SC-Sodium saccharine, MS-Magnesium stearate.

METHODS THE OPTIMIZATION

Effect of different disintegrants on disintegrating time of table:

The various disintegrants was used for determination of disintegrating time. Five different disintegrants was used in a different concentration when prepared tablet filler by direct comparison and hole technology method. Finally determine the disintegration time of tablet.

Table 1. Effect of disintegrants on disintegrating time

Batch	Ingredients (mg)								DST (sec)
	SCMC	SSG	Lactose	Mannitol	SS	MS	Talc	Camphor	
F1	7.0	7.0	-	7.0	-	2	2	100mg	82
F2	7.0	-	-	7.0	-	2	2	100mg	75
F3	-	7.0	-	7.0	7.0	2	2	100mg	122
F4	-	-	7.0	7.0	-	2	2	100mg	90
F5	-	-	-	7.0	-	2	2	100mg	44
F6	-	-	7.0	7.0	7.0	2	2	100mg	89

Where- SCMC- Sodium corboxy methyl cellulose, SSG- Sodium starch glycollate, SS- Sodium saccharine, MS-Magnesium stearate.

Optimization of disintegrants concentration:

From above the study three disintegrants was selected for further determination of actual concentration to quick disintegrants the tablet. Same filler and method used for preparation of tablet.

Table 2. Optimization of disintegrants concentration

Batch	Ingredients (mg)								DST (sec)
	SCMC	SSG	Lactose	Mannitol	SS	MS	Talc	Camphor	
F1	30			3	1.5	2	2	100	125±0.26
F2		30		3	1.5	2	2	100	112±0.96
F3	15	15	30	3	1.5	2	2	100	96±0.76
F4		15	15	3	1.5	2	2	100	130±0.44
F5	22		15	3	1.5	2	2	100	80±0.43
F6	11	22		3	1,5	2	2	100	82±0.36

Particle sizedetermination
The Particle size determination was done by optical microscopy. The result is shown in table.no.8.

Compatibility study of drug with excipients
Compatibility study of drug with excipients was performed. The result are shown in table.no.9**Pre- compressibility studies**

Bulk density (D_b)
Apparent bulk density was determined by bulk density apparatus. The result is shown inTtable.no.10

$\rho_b = M / V_b$
Where: ρ_b –bulk density-is the weight of powder drug, Vb-is the volume of powder drug.

Tapped Density
Apparent tapped density was determined by tapped density apparatus. The result is shown in table.no.10

$D_t = M / V_t$

Where, M is the mass of powder, Vtis the tapped volume of the powder.

Compressibility index %
The simplest way for measurement of free flow of powder is compressibility index was determine by this formula. The result is shown in Table.no.10
-

$$\% \text{ C.I.} = \rho_t - \rho_b / \rho_t \times 100$$

Where,ρ_b –bulk density, ρ_t –tapped density,CI-compressibility index.

Hausner ratio
It was studied by following formula. The result is shown in Table.no.10
-

$$\text{Hausner ratio} = \rho_t / \rho_t$$

Where Dt is the tapped density, $D_b$is the bulk density.

Angle of repose
The angle of repose was determined using funnel method. The result is shown in Table.no.10

$\tan(\Theta) = \tan^{-1} (h / r)$
Where, Θ is the angle of repose,'h' is the height in cms,'r' is the radius in cms.

Post compressibility studies

Thickness
The thickness of flurbiprofen was calculated by using Vanier calipers. The result is shown in Table.no.11

Hardness

In the present study the cracking strength of the tablet was measured using Monsanto hardness tester.Kg/cm2.The result is shown in Table.no.11

Uniformity of weight

I.P. procedure for uniformity of weight was followed. The weight variation test would be a satisfactory method of determining the drug content uniformity. The result is shown in Table.no.11

Friability test (F)

The friability of the tablet was determined by using Roche friability apparatus. The friability (f) is given by the formula. The result is shown in Table.no.11

$$F = (1- W_0 / W)_x 100$$

Where, W0is weight of the tablet before the test and W is the weight of the tablet after the test.

Wetting time

A piece of tissue paper folded twice was placed in a small Petridis containing 6 ml of water. The tablet was placed on the tissue paper and allowed to wet completely. The time required for complete wetting of the tablet was then recorded. The result is shown in Table.no.11

Water absorption ratio

A piece of tissue paper folded twice was placed in a small Petridis containing 6 ml of water. A tablet was put on the paper & the time required for complete wetting was measured. The wetted tablet was then weighed. H_2O absorption ratio, R, was determined using following equation, The result is shown in Table.no.11

$$R = 10 (W_a/ W_b)$$

Where-W_A is weight of table before water absorption. W_b is weight of tablet after water absorption.

Disintegration time

The test was carried out on 6 tablets using the apparatus specified in I.P. - 1996. Water at $37^oC \pm 2^oC$ was used as a disintegration media and the time in sec taken for complete disintegration of the tablet palatable mass remaining in the apparatus was measured in a sec. To comply the test all tablets should disintegrate within 3 min'. The result is shown in Table.no.11

Drug content analysis

Ten randomly selected tablets were weighed and average weight is calculated, the tablet was powdered in a glass mortar. The weight equivalent to 10 mg of flurbiprofen is weighed. The weighed amount is was taken and dissolved in 0.1 N HCl. After that an aliquot of the fill rate was diluted and analyzed sepctrophotometerically (double beam spectrophotometer) at 314 nm. The result is shown in Table.no.11

In-vitro drug release

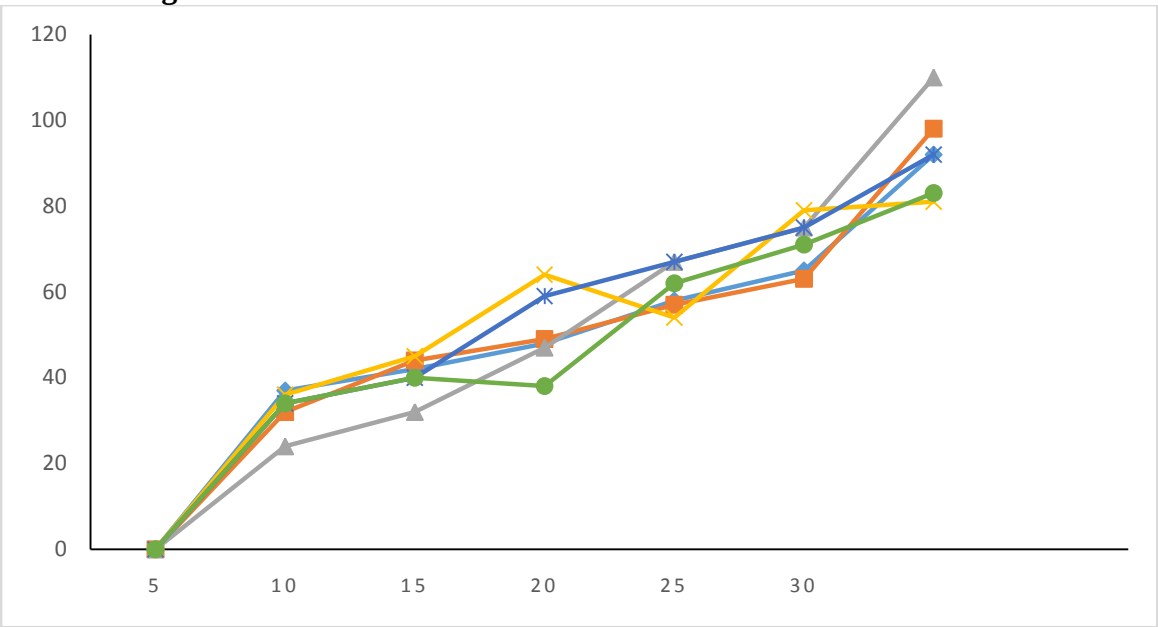

Fig. 4. In-vitro flurbiprofen release

In vitro drug release was found between 86 to 98 % within 30 min of the study. The formulation F5 containing sodium carboxy methyl cellulose and sodium starch glycollate in equal proportion has shown highest drug release (98± 0.88, R^2 =0.955%) within 30 min than other formulation. Result also revealed that formulation F5 having highest drug releases. And other like F3 and F1 was also good in vitro releasing shown.

In-vitro drug table

Table 12. In-vitro flurbiprofen release

Time in min	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
2	16.07	23.23	27.67	23.62	28.34	30.12
4	35.55	43.76	56.43	47.75	56.26	68.42
6	53.78	67.98	95	84.74	98.72	100.67
8	87.87	78.39	98.90	88.74	100.65	-
10	86.35	87.66	100	98.64	-	-
12	100.29	-	-	-	-	-

Effect of disintegrants on disintegrating time of tablet

The disintegrating time of tablet formulation was found 44 – 122 sec. Observed that the effect of disintegrating agent on the disintegrating time of tablet in a table. It shows that the combination of SSG, SCMC AND lactose starch in the tablet formulation F5 the disintegrating time should be quick (i.e. 14 seconds) as compare to other disintegrants in a table.1. Hence SSG, SSCMC and lactose has been selected for further formulation of rapid disintegrating tablets.

Optimized the concentration of selected disintegrating agents

The disintegrating time of table using different concentration of disintegrates was found 14 – 130 sec. It is observed that the disintegrating time of table quick in the concentration range 5-

10% of the selected disintegrating agents. This concentration range of disintegrants has been used for the formulation of rapid disintegrating tablet.

RESULTS AND DISCUSSION

Identification of drug by UV/Visible spectrophotometer

UV Spectrophotometric method was used for the analysis of flurbiprofen. The UV scan of the drug sample showed highest peak at 254 nm which is nearby to the standard value. This

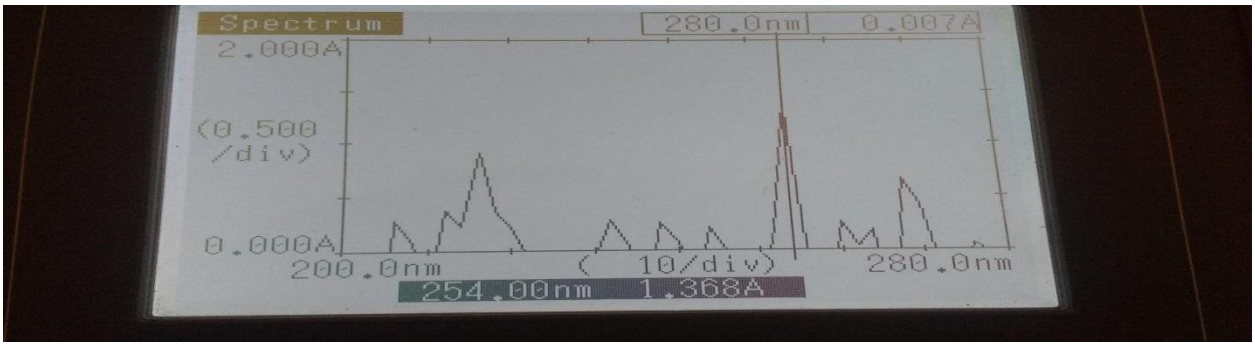

Fig. 1. Peak detection λ_{max} for flurbiprofen in chloroform

Standard curve of flurbiprofen in chloroform

Standard curve calibration of flurbiprofen was prepared in chloroform at 254 nm in UV spectrophotometer.

Standard curve of flurbiprofen:

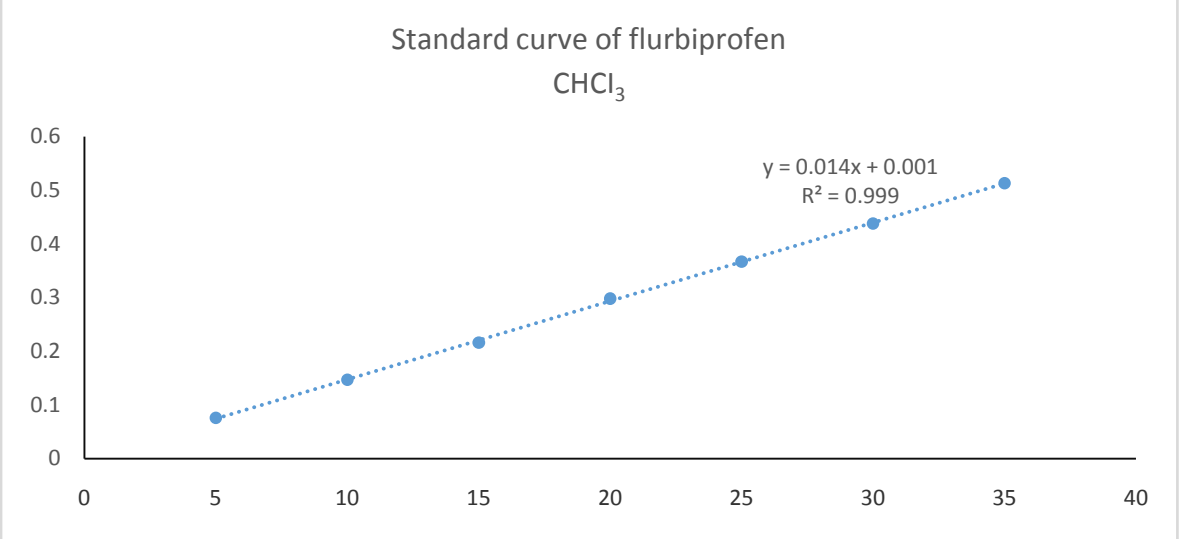

Fig 2. Standard curve calibration of flurbiprofen

Equation –

$Y = 0.0146_X + 0.001$

$R^2 = 0.9997$

X =Concentration in micro gram

For preparation of standard curve, solution of the drug sample were prepared in chloroform and there absorbance were measured at 254 nm the linearity range were found to be 2-14 mcg. /ml.

Table no.5.Determination ofmelting point\ Partition coefficient\pH

Melting point\ Partition coefficient\pH	
Melting point	108^{o}C -110^{o}C (drug is pure)
Partition coefficient	3.6-4 (drug is lipophilic)
pH determination	4.5 (acidic)

IR spectrum of flurbiprofen

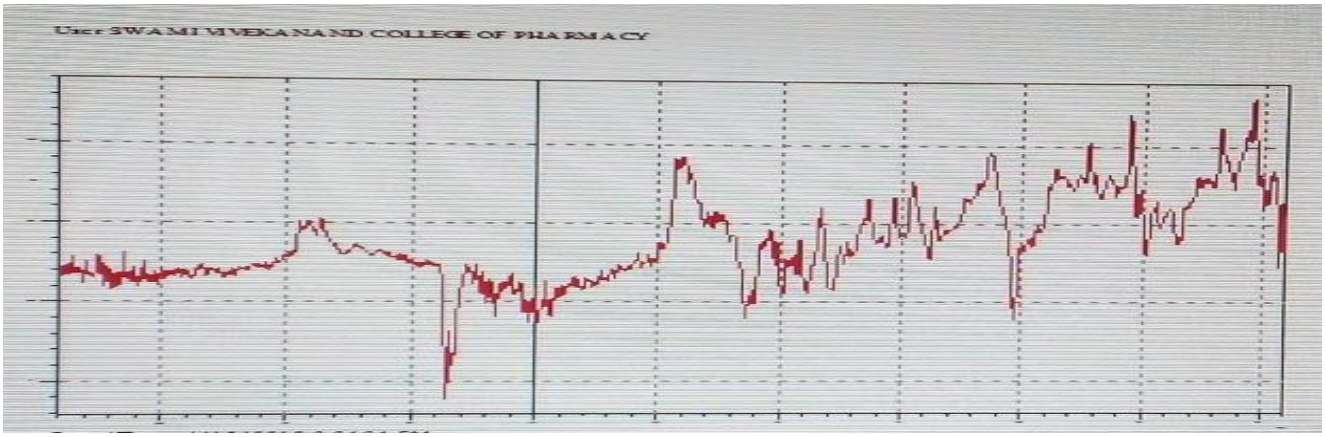

Fig. 3. IR spectrum of flurbiprofen drug sample

IR spectrum of drug sample has been interpreted and correlated with standard IR spectrum of flurbiprofen. There is no change in functional group of drug sample or same with standard shown in Figure it shows that the drug sample of flurbiprofen is pure.

Solubility Properties

Qualitative Solubility-

The value of qualitative solubility of flurbiprofen are shown below

Table 6. Qualitative solubility of flurbiprofen

Solvents	**Solubility Properties of the drug**
Distilled Water	+
Ethanol	+++
Chloroform	++++
Ether	+++
Acetone	++++

+ Insoluble, ++ poorly soluble, +++ slightly soluble, ++++ freely soluble

Qualitative solubility studies of drug shown in table 3 depicted that the drug is more soluble in organic solvent as compare to hydrophilic solvents so it can be concluded that drug is lipophilic in nature.

Quantitative solubility
The result of quantitative solubility of flurbiprofen are given below-

Table 7. Quantitative solubility of flurbiprofen

Solvent (1ml)	Concentration of drug in solvent
Distilled water	0.00 mg of drug was present in 1 ml of distilled water
Ethanol	6.50 mg of drug was present in 1 ml of ethanol
Ether	5.67 mg of drug was present in 1 ml of ether
$CHCI_3$	10 mg of drug was present in 1 ml of $CHCI_3$
Octanol	5.59 mg of drug was present in 1 ml of Octanol
pH 7.4	4.79 mg of drug was present in 1 ml of pH 7.4

Quantitative solubility studies shown in table 4 confirm that the drug more soluble in organic solvents.

Particle size
The result of the microscopic evolution for the measurement of particle size of the drug particles are given below in table.

Table 8. Particle size of flurbiprofen

S.No	Size Range	Mid-point (m.p)	No. of particle (N)	M.P × N	M.P×N×L.C
1	0-1	0.5	08	4	7.76
2	1-2	1.5	09	13.5	26.19
3	2-3	2.5	12	30	58.2
4	2-4	3.5	27	94.5	183.33
5	4-5	4.5	24	108	209.52
6	5-6	5.5	20	110	213.4
			∑n= 100		∑d=698.4

Least count (L.C) = 1.94
Particle size of flurbiprofen = ∑d \ ∑n
= 698.4 \ 100
= 6.98

Particle size was found to be 6.98 µm. Particle size distribution pattern depicted in fig. show that drug particle are distributed in range of 1-6 µm and maximum number of particle are present in size range of 4-6µm. This distribution pattern also indicates that the drug is amorphous in nature.

Compatibility study of drug with excipients by

Table 9. Flurbiprofen- excipients compatibility observations

Additives (100 mg each) with drug	Observation at 60^0C for 2 weeks	Observation at 40^0C for 2 months	Remarks
Drug flurbiprofen	No change	No change	Accepted
Drug + Lactose	No change	No change	Accepted
Drug+ Sodium starch glycollate	No change	No change	Accepted
Drug+ Sodium caboxy methyl cellulose	No change	No change	Accepted
Drug+ magnesium stearate	No change	No change	Accepted
Drug+ Mannitol	No change	No change	Accepted
Drug+ Sodium saccharine	No change	No change	Accepted

Compatibility studies of drug and excipients mixture was studied and observed physically. There is no changes in liquefaction, caking, Colour, odour, discoloration flurbiprofen.[25, 6, 2,11,9]

Pre- Compression parameter of formulation

Table 10. Evaluation of Mixed Blend of Flurbiprofen and Excipients

Formulation code	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Hausner ratio	Compressibility index (%)	Angle of repose
F1	0.681±0.005	0.832±0.003	1.24±0.12	12.05±0.15	27^o.22'±0.12
F2	0.683±0.006	0.831±0.003	1.22±0.15	12.49±0.16	26^o.92'±0.06
F3	0.680±0.003	0.834±0.001	1.24±0.18	12.43±0.12	23^o.44'±0.02
F4	0.685±0.008	0.833±0.003	1.23±0.12	12.38±0.14	24^o.32'±0.002
F5	0.687±0.005	0.891±0.007	1.26±0.13	12.32±0.15	23^o.44'±0.02
F6	0.688±0.005	0.875±0.003	1.21±0.12	12.49±0.13	26^o.25'±0.09

The Bulk density of all the formulation was within the range of 0.680±0.003 to 0.688±0.005gm. /ml and Tapped density was found to be in the range of 0.831±0.003 to 0.891±0.007 (good flow property). The angle of repose of powder blends of all formulation was found to be in the range of 24o.32'±0.002 to 27^o.22'±0.12 (good flow property). The calculated carrs index of all formulation was found to within the range of 12.05±0.15 to 12.49±0.16 (good flow property).The calculated Hausners ratio of all formulation was found to within the range of1.21±0.12 to 1.26±0.13 (good flow property). The values of pre-compression parameters evaluated were within the prescribed limits and indicated good free flowing properties.

Post-compression evaluation parameter of tablets

Table 11. Post-compression evaluation parameter of tablet by novel holetechnology

Evolution parameter	Formulation code					
	F1	F2	F3	F4	F5	F6
Thickness (mm)	3.89 ± 0.06	3.86 ± 0.08	3.92 ± 0.03	3.96 ± 0.04	3.89± 0.03	3.95 ± 0.07
Hardness (kg/cm^2)	3.25 ± 0.04	3.5 ± 0.03	3.00± 0.05	3.00 ± 0.04	3.25 ± 0.06	3.00 ± 0.03
Friability (%)	0.58 ± 0.07	0.56 ± 0.01	0.52 ± 0.02	0.53 ± 0.08	0.49 ± 0.06	0.52 ± 0.03
Weight variation	Passes	Passes	Passes	Passes	Passes	Passes
Wetting time (sec)	39 ± 0.54	30 ± 0.63	21 ± 0.49	42 ± 0.38	22 ± 0.64	32 ± 0.77
Diameter (mm)	6.85 ± 0.08	6.82 ± 0.08	6.81 ± 0.06	6.80 ± 0.05	6.83 ± 0.05	6.84 ± 0.06
Disintegration Time (sec)	17 ± 0.53	25 ± 0.51	32 ± 0.65	23 ± 0.65	14 ± 0.65	19 ± 0.25
% Drug Content	97 ± 0.77	90 ± 0.67	91 ± 0.97	96 ± 0.25	98 ± 0.74	90 ± 0.84
Hole depth (mm)	1.30 ± 0.03	1.31 ± 0.02	1.28 ± 0.04	1.27 ± 0.03	1.32 ± 0.02	1.24 ± 0.04

The post compression parameter of all batches was studied and show table no.8. The crushing strength of tablets prepared by holetechnology was within the range of 3.00 ± 0.03 to 3.25 ± 0.06kg/cm^2. The loss of percentage of weight in friability was found to be 0.49 ± 0.06 to 0.58 ± 0.07 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 of3.89± 0.03 to 3.96 ± 0.04 mm and 6.80 ± 0.05 to 6.85 ± 0.08 mm respectively. The hole depth of all formulation prepared by hole technology was found to be in range of 1.24 ± 0.04 to 1.32 ± 0.02 mm. The wetting time of all formulation prepared by hole technology was found to be in the range 21 ± 0.49 to 42 ± 0.38 sec. The disintegration time of all formulation prepared by hole technology was found to be in the range of 14 ± 0.65 to 32 ± 0.65 sec and was shown in table 8. The weight variation of all formulation prepared by hole technology was Passes. The drug content of all formulation prepared by hole technology was found to be in the range of 90 ± 0.67 to98 ± 0.74.

In-vitro drug release

The development of dissolution method for RTDs is comparable to the approach taken for conventional tablet, and is practically identical. Dissolution condition for drug listed in a pharmacopoeia monograph, is a good place to start with scouting runs for a bioequivalent RTD. Other media such as chloroform and buffer (pH-6.8) should be evaluated for OTD much in the same way as their ordinary tablet counter parts. The USP2 paddle apparatus has been used for this purpose which is the most suitable and common choice for rapid disintegrating tablets, with a paddle speed of 50 rpm commonly used. Typically the dissolution of RTD is very fast when using USP monograph condition; hence slower paddle speed may be utilized to obtain a profile. The USP 1 basket apparatus may have certain

application but some time tablet fragments or disintegrated tablet masses may become trapped on the inside top of the basket at the spindle where little or no effective stirring occurs, yielding irreproducible dissolution profiles. In vitro dissolution studies of rapid disintegrating tablet of flurbiprofen and commercial conventional tablet was perform according to USP XXIII Type-II dissolution apparatus employing a paddle stirrer at 50 rpm using 900 ml of 6.8 phosphate buffer at 37±0.5^{o} as dissolution medium. One tablet was used UN each test. Aliquots of the dissolution medium (5ml) were withdrawn at specific time intervals (5, 10, 15, 20,25and 30 min) and replaced with the equal volume of fresh medium. The samples was filtered through 0.22 um membrane filter disc and analyzed for drug contain by measuring the absorbance at 254nm. Drug concentration was calculated from the standard calibration curve and expressed as percent drug dissolved.[1, 4,5,6,25,11]

CONCLUSION

Rapid dissolving tablets are the general from of nomenclature for tablet that disintegrate rapidly or instantly run the oral cavity. RDTs have better patient acceptance and compliance and may offer improved biopharmaceutical properties, improve efficacy, and better safety compared with cointentional oral dosage forms. RDTs can be prepared in different ways and product performance depends upon the drug suitability and excipients selections in the delivery system. In combination with other technologies such as modified release and microencapsulation, RDTs will continue to provide enhanced commercial and therapeutic benefits. RDT is a growing technology, offering considerable benefits for lifecycle management[16], development timelines, patient convenience and market share. By paying close attention to advance in technologies, pharmaceutical companies can take advantage of RDTs for product line ex-tensions or for first-to-market products. With continued development of new pharmaceutical excipients, one can expect the emergence of more novel technologies for RDTs in the days to come. The successful marketed RTDs have good taste and rapid release properties. With rapid acceptance of RTDs by patients and pharmaceutical companies, the market for this dosage from is promising, and the product pipeline continues to grow rapidly.

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