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Formulation and Evaluation of Diclofenac Sodium Effervescent Tablets

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ABSTRACT

The main objective of present work is to formulate and evaluate Diclofenac sodium Effervescent tablets. Diclofenac sodium is an established analgesic developed for rapid absorption, which may be beneficial in treating acute migraine. Diclofenac sodium Effervescent tablets was prepared using excipients like sodium bicarbonate, citric acid, mannitol, sodium benzoate, talc, vanillin and varying concentrations of Sodium starch glycolate and croscarmellose using direct compression technique. The powder blend of all formulations were evaluated for angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio. All the prepared formulations were tested for physical parameters like weight variation, thickness, hardness, friability ,assay ,effervescence time, wetting time and P^H and found to be within the pharmacopoeia limits .Optimized formulation was selected based on the criteria the max amount of drug release within 9 min. Among six formulations F3 was found to be the best formulation as more than 90% of drug is released within 9 min compared to other formulations. The drug release profiles of optimized Diclofenac sodium effervescent tablets was compared with that of dispersible marketed product and it was observed that the drug release from effervescent tablets was much faster than that of marketed dispersible tablets.

Keywords: Effervescent tablets, Diclofenac sodium, Direct compression method, In vitro dissolution studies

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INTRODUCTION

Oral administration is the most popular route about 50-60% of total dosage forms are administered due to ease of ingestion, pain avoidance, versatility (to accommodate various types of drug candidates), and most importantly patient compliance[1]. Solid oral delivery systems do not require sterile conditions and are therefore less expensive to manufacture [2.] Many pharmaceutical dosages are administered in the form of liquids, granules, powders , and pills. Generally a pill design is for swallowing intact or chewing to deliver a precise dosage of medication to patients. The pills, which take in tablets and capsules, are able to retain their shapes under moderate pressure. However some patients particularly paediatric and geriatric patients have difficulty in swallowing or chewing solid dosage forms [3]. Medications such as pills are the forms generally used, whereas they have some disadvantages. Slow absorption is the important disadvantage as the onset of action gets pro longed. In liquid forms of the medication, the delay is avoided. Many drugs do not have enough stability levels in the suspension form. Gastric residence also affects drug delivery which is predicted before. Gastro-retentive preparations are created to manage gastric residence. Another form of the drugs is effervescent tablets [4]

Oral forms are more preferred way of medication compared to other routes of administration. The main disadvantage with this dosage form is slow absorption .When taking the liquid form, the lower dosages can be used. Stability of active pharmaceutical ingredients is lower in liquid form. As effervescent tablets are dissolved in water just before administration, it provides advantage for the stability of these medications [4] Taking big tablets or capsules is difficult for the patients. Effervescent technology provides an alternative to them. Tablets takes more time to dissolve in the stomach. In effervescent, ingredients are distributed in the solution and they are not localized in certain point. They can be use with liquids and promotes patients to take more liquid. Absorption is improved and usage is easy in effervescent tablets. [5]

Advantages of Effervescent Tablets

Improved taste, faster absorption, presentable fizzy tablets.

Disadvantages of effervescent tablets:

Larger tablets, complex production process, delicate packaging process.[6]

Effervescent granules are usually prepared from a combination of Citric acid and Tartaric acid Effervescent salts include the following ingredients, which actually produce the effervescence, Sodium bicarbonate, Citric acid and Tartaric acid. When added to water the acid and base react to liberate carbon dioxide, resulting in Effervescence. It should be noted that any acid-base

combination which results in the liberation of carbon dioxide could be used in place of this combination as long as the ingredients are suitable for pharmaceutical use.[7]

With a prevalence of 8% in males and 12–15% in females migraine is one of the commonest issues encountered in primary practice. Migraine is characterized by recurrent attacks of pulsatile, unilateral headache often accompanied by nausea and vomiting, photo- and phonophobia. In about 20% of patients the headache is proceeded by an aura consisting of transient neurological symptoms, most frequently a scintillating scotoma.

An estimated 10–20% of NSAID patients experience dyspepsia. Most of the Nonsteroidal anti-inflammatory drugs were associated with serious upper gastrointestinal adverse events, including bleeding. Over the past decade, deaths associated with gastric bleeding have declined. To overcome this problems effervescent drug delivery systems in invented.

Migraine is a common, disabling condition and a burden for the individual, health services and society. Most of the patients unable to, seek professional help and rely on over-the-counter (OTC) analgesics. Simple analgesics like NSAIDs, or combination analgesics are given first choice agents if the patients has mild to moderate migraine attacks not associated with vomiting or severe nausea .NSAIDs or analgesics are preferred because they are effective, less expensive, and less likely to cause adverse effects than migraine-specific agents such as triptans or ergots .When mild to moderate attacks are associated with severe nausea or vomiting, rectal or an oral antiemetic drug can be used in conjunction with simple or combination analgesics. NSAIDs usage in migraine is consequent from their analgesic properties in other pain disorders and supported by the indirect indication that prostaglandins are involved in migraine pathophysiology [8]

Diclofenac sodium (DS) is a non-steroidal anti-inflammatory drug, widely used to control pain and for the treatment of rheumatic arthritis . The conventional immediate-release DS tablets make the drug immediately available for absorption in upper gastrointestinal (GI) tract resulting in local GI toxicity. It has been reported that the GI toxicity is not only caused by the inhibition of the prostaglandin synthesis, but is probably also due to direct contact of the drug with the mucosa [9]

To cope with the problem, extensive efforts have been made for the formulation of diclofenac sodium Effervescent tablets. Effervescent tablets are administrated in liquid form, they are easily swallowed so that they are preferred over tablets or capsules with a difficult consumption for some patients. On the other hand, one dose of effervescent tablet is regularly dissolved in 3-4 ounces of water. Being earlier dissolved in a buffer solution, effervescent products do not get in direct contact with the gastrointestinal tract and well tolerated in stomach and intestine due to reduced gastrointestinal irritation. Another advantage regarding effervescent tablet is that when they are

taken by the patient, exactly the taken amount enters the stomach. In fact, the CO_2 produced in an effervescence reaction will increases the penetration of active substances into the paracellular pathway and consequently their absorption.[10]

MATERIALS AND METHOD

Diclofenac sodium (Hetero drugs Ltd, Hyderabad, India),Sodium bicarbonate(Qualikems. Fine chem. Ltd, Vadodara, India),Citric acid(Qualikems Fine Chemicals Pvt. Ltd, India),Mannitol(Finar chemicals PvtLtd, Ahmedabad, India),Sodium starch glycolate(Finar chemicals Pvt Ltd, Ahmedabad, India),Croscarmellose (Finar chemicals PvtLtd, Ahmedabad, India),Sodium benzoate(Qualikems. Fine chem. Ltd, Vadodara, India),Saacharin(Central drug house (P) Ltd, new Delhi, India),Talc (Loba cheimepvt Ltd, India),Vanillin (Qualikems. Fine chem. Ltd, Vadodara, India) and all other reagents used are of analytical grade.

Calibration curve of Diclofenac sodium

100mg of Diclofenac was dissolved in 10ml of methanol in a 100ml volumetric flask and the volume was made up to 100ml using phosphate buffer from this stock 10ml was transfer to another volumetric flask made up to 100ml with phosphate buffer from this secondary stock samples were taken separately and made up to 100ml with to produce 2,4,6,8,10,12,14µg/ml respectively. The absorbance was measured at 276nm.by using UV-visible spectrophotometer.

Preparation of Diclofenac sodium Effervescent tablets:

All ingredients were weighed accurately according to their respective formulations as presented in Table 1. They were sifted through a stainless steel mesh with a pore size of 0.85 mm and were blended for 15 min at 20 rpm. Tablets were prepared by compressing powder blend using rotary compression machine with round flat 13 mm round punches.

Table 1: Composition of Diclofenac sodium Effervescent tablets

Ingredients(mg)	F1	F2	F3	F4	F5	F6
Diclofenac sodium	50	50	50	50	50	50
Sodium bicarbonate	150	150	150	150	150	150
Citric acid	115	115	115	115	115	115
Sodium benzoate	18	18	18	18	18	18
Sodium saacharin	30	30	30	30	30	30
Sodium starch glycolate	-	18	30	-	-	15
Crosscarmellose sodium	-	-	-	18	30	15
Mannitol	233	215	203	215	203	203
Talc	4	4	4	4	4	4
Flavour	q.s	q.s	q.s	q.s	q.s	q.s
Total weight	600	600	600	600	600	600

Pre-compression parameters:

Bulk density (D_b):[11]

It is defined as the ratio of total mass of powder to the bulk volume of powder. It is determined by transferring the weighed quantity of powder in to a graduated cylinder and then note down the bulk volume. Bulk density is calculated according to the formula mentioned below and is expressed in terms of g/ml and is given by,

$$D_b = M/v_b$$

Where, M is the mass of powder

v_b is the bulk volume of powder.

Tapped Density :

It is defined as the ratio of total mass of powder to the Tapped volume of powder .It is measured by tapping the powder for 100 times and the tapped volume was noted if the difference between these two volumes is less than 2%.if it is more than 2%,tapping is continued for 150 times and the tapped volume was noted. tapping was continued until the difference between successive volumes is less than 2% it is expressed in g/ml and is given by,

$$D_t = M/V_t$$

Where, M is the mass of powder

V_t is the tapped volume of the powder.

Angle of Repose(θ):

It is defined as maximum angle possible between the surface of the pile of the powder and the horizontal plane

$$\tan(\theta) = h/r$$

$$\theta = \tan^{-1} h/r$$

Where, **θ** is the angle of repose.

h is the height in cm; r is the radius in cm

The powder mixture was allowed to flow through the funnel which is previously fixed to a stand at definite height (h).The angle of repose was then calculated by measuring the height of the pile and radius of powder formed.

Carr's index (or) % compressibility:

It indicates powder flow properties. It is expressed in percentage and is given by,

$$I = Dt - Db/Dt * 100$$

Where, Dt is the tapped density of the powder and

Db is the bulk density of the powder

Hausner ratio:

Hausner ratio is an indirect index of ease of powder flow it is calculated by the following.

Formula: Hausner ratio=Dt/Db

Where: Dt is the tapped density of the powder and

Db is the bulk density of the powder

Post compression parameters:

Weight variation[12]

Weight variation was calculated as per method describe in USP. 20 tablets were weighed individually and the average weight is calculated. The requirements are met if the weights of not more than 2 of tablets differ by more than the percentage

Thickness:

Three tablets from each batch were taken and individual tablet thickness was measured by using digital vernier caliper. It is expressed in mm. Average thickness and standard deviation values were calculated.

Hardness:[13]

Hardness indicates the ability of a tablet to resist mechanical shocks during handling. The Hardness of tablets was determined using a Pfizer hardness tester. It is expressed in kg/cm^2. Three tablets from each batch were analyzed for hardness. The mean and standard deviation were also calculated.

Friability

20 tablets from each batch were selected randomly and weighed. These pre weighted tablets were subjected to friability testing using Roche friabilator for 100 revolutions at 25 rpm and dropping a tablet at height of 6 inches in each revolution. Tablets were removed, de-dusted and weighed again.

$$\% \text{ Friability} = (W_1 - W_2) \times 100/W_1$$

Where W_1= Initial weight of the 20 tablets.

W_2 = Final weight of the 20 tablets after testing.

Effervescence time of tablets (disintegration time)[14]

Effervescence time was determined as per European pharmacopeia, by allowing one tablet to disperse completely in 200 ml of purified water at room temperature. Time required for the completion of effervescence was noted using a digital stopwatch. Effervescence time determination was performed for 6 tablets and results were presented as average ±S.D.

Wetting time of tablets

Wetting time of the tablets from each formulation was determined by placing the tablet on a filter paper soaked in a watch glass containing 5 ml purified water. The time required for complete hydration of the tablet was noted with a digital stop watch . The experiment was performed in triplicate for each formulation and average waiting time was calculated.

In Vitro release studies

The *In vitro* dissolution studies of the developed formulations were carried out using USP apparatus type II at 50 rpm. The dissolution medium consisted of 900 ml of phosphate buffer pH 6.8 and maintained at 37°c ± 0.5°c. The drug samples are collected at different time intervals 3,6,9,12,15 min and the samples are analysed by using UV-visible spectrophotometer

P^H of solution

One tablet was dissolved in purified water. After complete dissolution, the solution pH was measured by Using a pH meter, the pH of the solution was measured by dissolving 3 tablets in 3 beakers containing 200 ml of water.

Assay:

10 tablets were weighed and triturated the tablet triturate equivalent to 50mg of drug was weighed accurately, dissolved in P^H 6.8 phosphate buffer and dilute to 100ml with same and then filter the solution and check the absorbance of solution using uv spectrophotometer.

RESULTS AND DISCUSSION:

The λ_{max} of Diclofenac sodium in P^H 6.8 was scanned and found to be at 276nm. The standard graph of Diclofenac sodium in phosphate buffer was plotted by taking concentration ranging from 2µg/ml to 14µg/ml on x-axis and absorbance on y-axis and a good correlation was obtained with R^2 values of 0.999 shown in Figure 1.

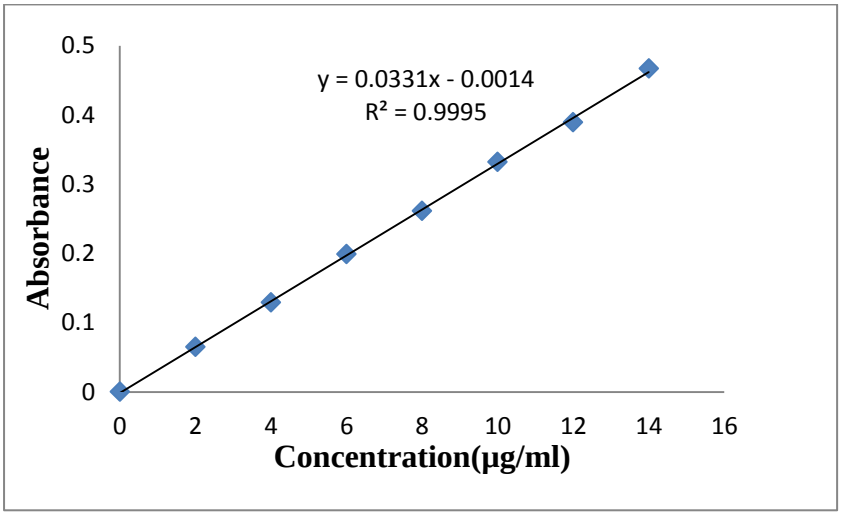

Figure 1: Calibration curve of Diclofenac sodium in phosphate buffer pH 6.8.

Pre-compression parameters:

The powder blend of all formulations were evaluated for angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio shown in Table.2. The results showed that the angle of repose for all the formulations blend was found to be in the range of 27.09±1.21 to 29.54±1.42.This indicates excellent to good flow property. Compressibility index was found to be in the range of 10.163 to 11.213. Hausner's ratio was found to be in the range of 1.078±0.009 to 1.14±0.005. This indicates good flow property.

Table 2:Pre-compression parameters of powder blend

Formulation Code	Bulk density(gm/ml)	Tap density(gm/ml)	Carr Index(%)	Hausner's ratio	Angle of repose
F1	0.833±0.02	0.901±0.05	10.163	1.082±0.004	28.28±1.11
F2	0.833±0.03	0.909±0.03	11.213	1.10±0.006	29.54±1.42
F3	0.832± 0.02	0.924± 0.07	11.058	1.14±0.005	27.41±1.09
F4	0.833± 0.04	0.912± 0.05	10.484	1.11±0.009	28.79±1.21
F5	0.826±0.08	0.915±0.03	10.775	1.078±0.009	27.09±1.21
F6	0.83 ±0.06	0.922±0.02	11.084	1.12±0.009	28.99±1.21

Post compression parameters:

All the prepared formulations were tested for physical parameters like weight variation, thickness, hardness, friability, assay, Effervescence time, surface pH and found to be within the pharmacopoeia limits the results of the tests were shown in the Table 3. Physically tablets from all the batches were very elegant. Their surface was smooth and shiny without sticking and picking indicating proper lubrication of powder blend. Thickness of the tablets from all formulations was within the range of 3.5–3.8 mm. No significant variation was observed in the thickness of tablets from different formulation. Friability of the tablets from all the formulations was within the official limits (British Pharmacopoeias, 2008) that was less than 0.8%.

Table 3a: Post compression parameters of tablets

Formulation Code	Weight variation(mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Assay (%)
F1	601±5.31	4.5±0.52	3.4±0.03	0.49±0.03	98.16±0.68
F2	598±4.98	4.7±0.59	3.8±0.11	0.51±0.01	99.25±0.54
F3	604±4.53	4.6±0.55	3.6±0.10	0.52±0.02	98.34±0.69
F4	599±4.38	4.9±0.51	3.9±0.08	0.35±0.04	99.24±0.85
F5	590±4.38	4.9±0.51	3.4±0.08	0.35±0.04	99.24±0.85
F6	603±4.38	4.9±0.51	3.5±0.08	0.35±0.04	99.24±0.85

Each value represents the Mean ±SD (n =3).

Table 3b: Post compression parameters of tablets

Formulation code	Effervescence time(sec)	Wetting time(sec)	P^H
F1	121±3	180±3	6.71±0.01
F2	63±5	148±3	6.83±0.04
F3	31±4	144±4	6.76±0.06
F4	73±4	172±3	6.81±0.03
F5	56±2	168±2	6.79±0.02
F6	42±3	148±4	6.80±0.05

Each value represents the Mean ±SD (n =3).

When disintegrant was added along with an acid/base pair, it enhanced effervescence reaction. It was much more vigorous as compared to that without disintegrant. In a higher concentration croscarmellose sodium absorbed water and formed a gel like material. The core of the tablet remained intact and the inner portion of the tablet got slowly exposed to water and the rate of effervescence reaction got reduced. SSG produced a concentration dependent decrease in effervescence time with both CA/SBC. At lower concentrations (3% w/w) a drop in disintegration time by SSG was smaller than that caused by the same concentration of croscarmellose sodium. But at a higher concentration (5%w/w), SSG was more efficient than crosscarmellose sodium shown in Figure 2. A drop in disintegration time by SSG at a higher concentration was larger than the drop caused by croscarmellose sodium with both acid/base pairs. Effervescence time decreases with increasing concentration of superdisintegrants. Among all formulation effervescence time is more for F1 formulation i.e.121±3 sec and less for F3 formulation i.e. 31±4 sec .Among all formulation Wetting time is more for F1 formulation i.e. 180±3 sec and less for F3 formulation i.e. 144±4. P^H of all formulations was found to be 6.71±0.01 to 6.83±0.04.

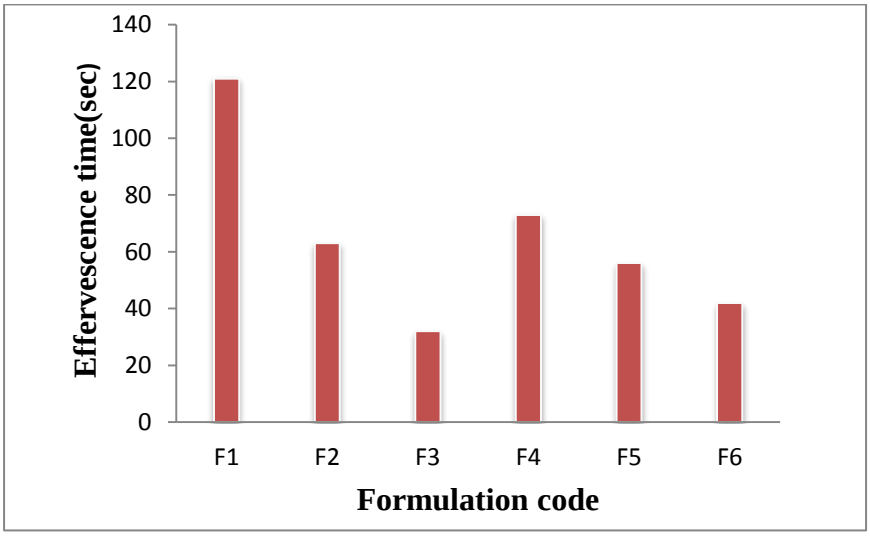

Figure 2: Effervescence time of tablets

***In vitro* dissolution studies**

From the *In vitro* drug release study the results were given in Table.4& Table.5, it was observed that formulations containing SSG the drug release was found to be faster compared to croscarmellose. High concentration of superdisintegrants used in the formulations caused high percent release of drug, while lower concentration caused low release. Thus, the release characteristics were significantly influenced by the type and concentration of superdisintegrants used. In case of F1 the drug release was less that is 52.39% within 15min due to lack of superdisintegrants. In case of formulations F2, F3 Varying concentrations of SSG was used that is.3% &4% and the % drug release was found to be 98.6% and 99.19% within 15min.In case of formulations F4,F5 Varying concentrations of croscarmellose was used i.e.3% &4% and the % drug release was found to be 96.45 and 97.44 within 15min.In case of formulations F6 equal concentrations of both SSG and croscarmellose that is 2.5%and the % drug release was found to 93.69%. Optimized formulation was selected based on the criteria that is the max amount of drug release within 9 min. Among six formulations F3 was found to be the best formulation that is more than 90% of drug is released within 9 min compared to other formulations. The drug release profiles of formulations shown in Figure 3.and Figure 4.

Table 4: *In vitro* dissolution data of Diclofenac sodium effervescent tablets of formulations F1-F3

Time(min)	F1	F2	F3
0	0±0	0±0	0±0
3	4.13±2.34	22.3±2.85	44.04±2.57
6	16.23±4.28	52.45±2.86	70.73±4.28
9	28.54±2.85	75.69±3.42	92.34±3.13
12	39.55±4.65	87.55±4.48	98.99±2.69
15	52.39±2.79	98.6±2.26	99.19±2.18

Each value represents the Mean ±SD (n =3).

Table 5 : *In vitro* dissolution data of Diclofenac sodium effervescent tablets of formulations F4-F6

Time(min)	F4	F5	F6
0	0±0	0±0	0±0
3	18.98±1.34	38.91±2.85	17.072±2.57
6	43.65±2.28	61.66±2.16	37.78±3.28
9	70.76±2.15	83.98±2.42	55.23±3.13
12	81.12±1.65	90.71±2.48	77.11±2.69
15	96.45±1.79	97.44±2.21	93.69±2.78

Each value represents the Mean ±SD (n =3).

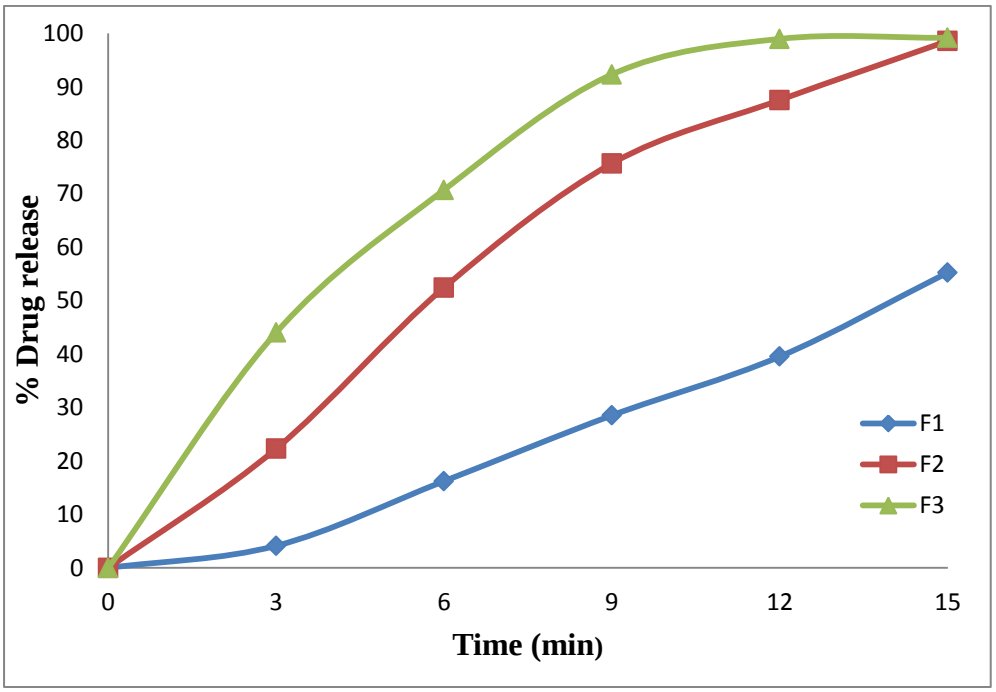

Figure 3: Dissolution profiles of formulation F1-F3

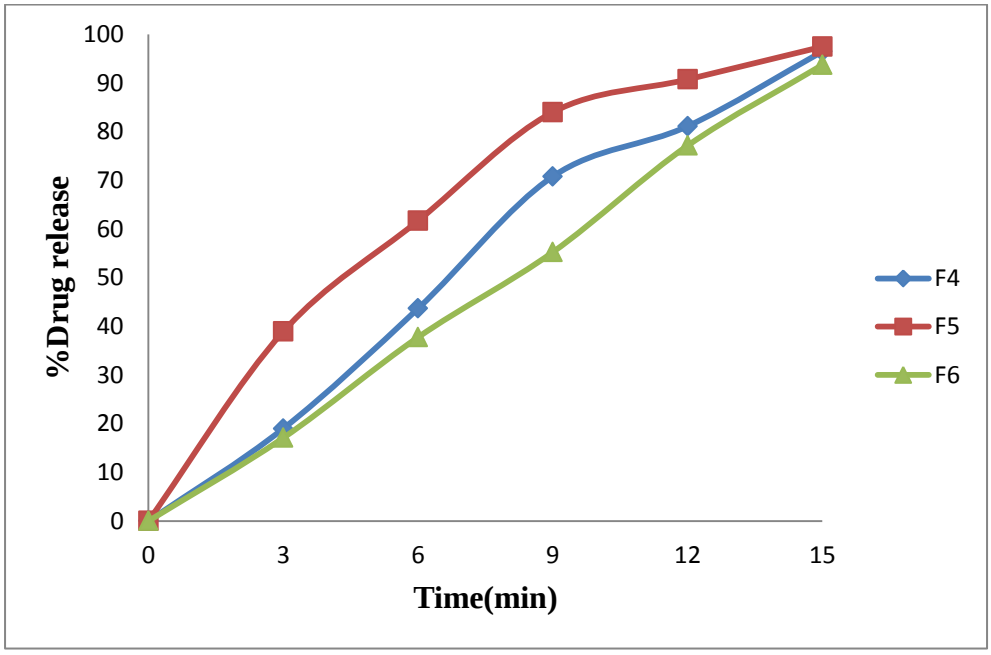

Figure 4: Dissolution profile of formulation F4-F6

Comparison of *In-vitro* dissolution profile of optimized formulation with Marketed Product:

The drug release profiles of optimized Diclofenac sodium Effervescent tablets was compared with that of dispersible marketed product i.e. Diclotal-DT shown in Table 6. Based on profiles it was observed that the drug release from effervescent tablets was much faster than that of dispersible tablets shown in Figure 5.

Table 6: Comparison of *In vitro* dissolution profile of optimized formulation with Marketed Product

Time(min)	F3	MP
0	0±0	0±0
3	44.04±2.57	14.67±2.85
6	70.73±4.28	32.55±2.16
9	92.34±3.13	54.77±2.42
12	98.99±2.69	78.91±2.48
15	99.19±2.18	95.6±2.21

Each value represents the Mean ±SD (n =3).

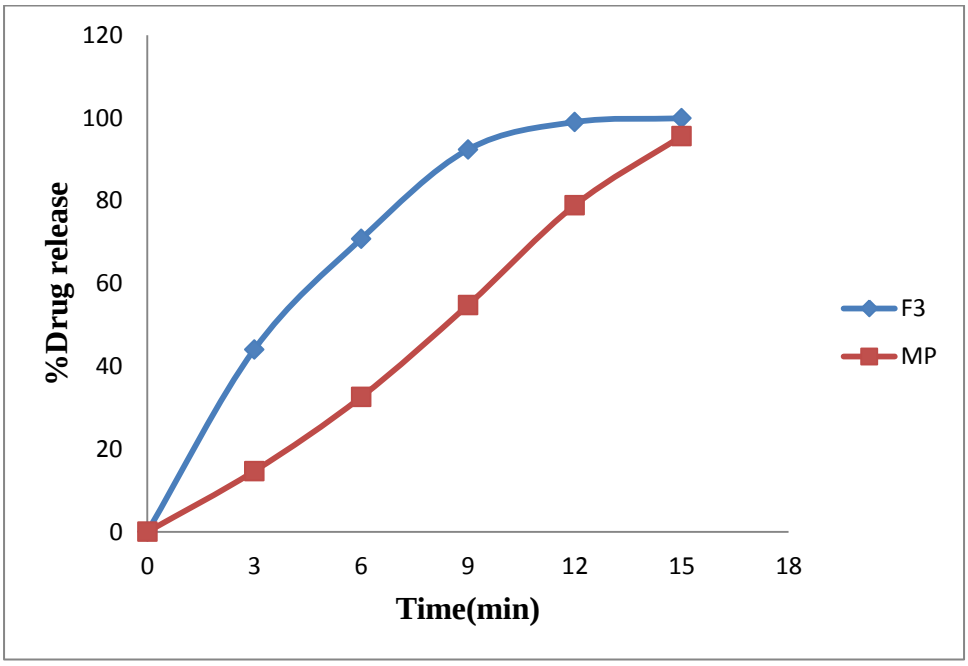

Figure 5: Comparison of *In vitro* Dissolution profile of optimized formulation with Marketed Product

CONCLUSION:

Diclofenac sodium Effervescent tablets was prepared using excipients like sodium bicarbonate, citric acid, Mannitol, sodium benzoate, talc, vanillin and varying concentrations of SSG and croscarmellose using direct compression technique The powder blend of all formulations were evaluated for angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio. All the prepared formulations were tested for physical parameters like weight variation, thickness, hardness, friability, assay ,effervescence time, wetting time and P^H and found to be within the pharmacopoeia limits .Optimized formulation was selected based on the criteria i.e. the max amount of drug release within 9 min Among six formulations F3 was found to be the best formulation i.e. more than 90% of drug is released within 9 min compared to other formulations.

The drug release profiles of optimized Diclofenac sodium Effervescent tablets was compared with that of dispersible marketed product it was observed that the drug release from effervescent tablets was much faster than that of dispersible tablets. Diclofenac sodium Effervescent tablets is an established analgesic developed for rapid absorption, which may be beneficial in treating acute migraine

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