ejpmr, 2023,10(9), 01-06

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

FORMULATION AND EVALUATION OF DICLOFENAC ORODISPERSIBLE TABLETS

Mahmoud Mahyoob Alburyhi*[1], Abdalwali Ahmed Saif[1], Maged Alwan Noman[1], Sami Ahmed Saeed[2] and Mokhtar Abd-hafiz Al-Ghorafi[3]

[1]Professor of Pharmaceutics and Industrial Pharmacy, Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Sana'a University, Sana'a, Yemen.
[2]Assistant Professor of Pharmaceutics and Industrial Pharmacy, Pharmacy Department, Taiz University, Taiz, Yemen.
[3]Associate Professor of Pharmaceutical Chemistry and Pharmaceutical Organic Chemistry Department, Faculty of Pharmacy, Sana'a University, Sana'a, Yemen.

***Corresponding Author: Mahmoud Mahyoob Alburyhi**
Professor of Pharmaceutics and Industrial Pharmacy, Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Sana'a University, Sana'a, Yemen.

Article Received on 23/06/2023 **Article Revised on 13/07/2023** **Article Accepted on 03/08/2023**

ABSTRACT

Diclofenac Free Acid was chosen to be the active pharmaceutical ingredient (API) in a Orodispersible tablets ODTs formulation, being a model of nonsteroidal anti-inflammatory drugs (NSAIDs). Diclofenac Free Acid is widely used as an analgesic, and being so, the faster the effect, the better the dosage form. The present study was aimed to formulate, evaluate and optimized a tablet which disintegrates and Orodispersible to show a rapid onset of action. In the present study, attempt has been made to prepare ODTs of Diclofenac Free Acid using superdisintegrants like croscarmellose sodium, and/or crospovidone in different ratios by direct compression. The prepared batches of tablets were evaluated for weight variation, hardness, friability, disintegration time, wetting time and *in-vitro* drug release which tested in comparing with standard drug. Among the all formulations F4 formulation was found to be showed improved drug release characteristics.

KEYWORDS: Orodispersible tablets, Diclofenac Free Acid, Anti-inflammatory drug, Superdisintegrants.

INTRODUCTION

Oral drug delivery has been known as the most widely used route of drug administration when compared to all the other routes that have been explored for delivery of different dosage forms to systemic circulation.[1-5]

The reason for such popularity of oral route may be attributed to its ease of administration. Recent advances in novel drug delivery systems (NDDS) aim at formulating a convenient dosage form for administration and to achieve better patient compliance to enhance safety and efficacy of drug molecules. One such approach is Orodispersible tablet. [6-9]

An oral fast dissolving drug delivery system is a novel tablet dosage form, which dissolves or disintegrates in the oral cavity with a good taste and flavor increasing the acceptability of bitter drugs without the need of water or chewing and hence called melt in mouth tablets or Orodispersible or rapid disintegrating or quick dissolving tablets. The drugs may be absorbed from mouth, pharynx or esophagus while the saliva passes down into stomach. Advantages of the fast dissolving tablets include rapid onset of action, ease of swallowing without the aid of water, enhanced dissolution rate, increased gastric absorption, minimized first pass metabolism, improved oral bioavailability and improved patient compliance. ODTs formulation combines the advantages of both conventional tablets and liquid formulations.[10-13]

Solid dosage forms are popular because of low cost, ease of administration, accurate dosage self-medication, pain avoidance, and the most importantly the patient compliance. The most prevalent solid dosage forms are being tablets and capsules. One essential downside of such dosage forms is Dysphagia (trouble in gulping) is basic among all age gatherings. Normal grumblings about the trouble in gulping tablets are size, surface, and taste of tablets. Geriatric and pediatric patients and voyaging patients, who might not have prepared access to water, are most needing simple gulping dosage forms. To satisfy these medicinal needs, pharmaceutical technologists have built up a novel oral dosage form known as Orodispersible tablets (ODTs) which disintegrate quickly in salivation, normally inside only seconds, without the need to take water. ODTs releases the medicament in the mouth for absorption through local oromucosal tissue and through pre-gastric (oral cavity, pharynx, and esophagus), gastric (stomach), and post-gastric (small and large intestine) segments of gastrointestinal tract.[14-18]

European pharmacopoeia defines ODTs as "Orodispersible tablets are uncoated tablets intended to

be placed in the mouth where they disperse rapidly before being swallowed".[10]

To develop a chemical entity, a lot of money, hard work and time are required. So focus is rather being laid on the development of new drug delivery systems for already existing drugs, with enhanced efficacy and bioavailability, thus reducing the dose and dosing frequency to minimize the side effects. For most therapeutic agents used to produce systemic effects, the oral route still represents the preferred way of drug administration, owing to its several advantages and high patient compliance compared to many other routes. Tablets and hard gelatin capsules constitute a major portion of drug delivery systems that are currently available.[11]

One important drawback of these dosage forms however is the difficulty to swallow. It is estimated that 35% of the population is affected by this problem which results in a high incidence of non-compliance and ineffective therapy. [12]

Orodispersible tablets disintegrate within 3 minutes. The performance of ODTs depends on the technology used in their manufacture. The orally disintegrating property of the tablet is attributable to a quick intake of water into the tablet matrix, which creates porous structures and result in rapid disintegration. Hence the basic approaches to develop ODTs include maximizing the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent and using highly water-soluble excipients in the formulation. Most fast dissolving delivery system tablets should include substances to mask the taste of the active ingredient. This masked active ingredient is then swallowed by the patient's saliva along with the soluble and insoluble excipients.[19,20]

In the present study, it was proposed to formulate Orodispersible tablets of Diclofenac Free Acid by using direct compression technique, with the aim of reaching high serum concentration of the drug in a short time period. In this study, effort has been made to formulate the fast dissolving tablets using super dis-integrant like croscarmellose sodium.

MATERIALS AND METHODS

Diclofenac Free Acid gift from (Shephaco Pharmaceutical Industry Company-Yemen). While Mannitol, Microcrystalline Cellulose (Avicel), Croscarmellose Sodium, Crospovidone, Sucralose, Peppermint Flavor Powder, Lactose Anhydrous, Citric Acid Anhydrous, Colloidal Silicon Dioxide (Areosil), Magnesium Stearate, Sodium Starch Glycolate, Hydroxy Propyl Methyl Cellulose, Xylitol, Pregelatinized Starch gift from (Modern Pharmaceutical Company -Yemen).

Formulation of ODTs

Formula (F1) consist of croscarmellose and crospovidone as superdisintegrants, mannitol as sweeting and cooling agent, sucralose as sweeting agent, colloidal silicon dioxide (Aerosil) as glidant, magnesium stearate as lubricant and anti-adherence, microcrystalline cellulose as diluent, Peppermint as flavoring agent were used. Formula (F2) consist of xylitol was used as sweeting, cooling agent and Pregelatinized starch as diluent and disintegrant.

Table 1: Ingredients Used in The Preparation of F1 and F2 Diclofenac Free Acid ODTs.

		F1				F2			
No	**Materials**	**Theoretical Amount**	**Actual Amount**	**Total Amount**	**Percentage %**	**Theoretical Amount**	**Actual Amount**	**Total Amount**	**Percentage %**
1	**Diclofenac Free Acid**	46.50 mg	47.13mg	9.43g	23.57%	46.5mg	47.133mg	9.43g	23.57%
2	**Croscarmellose Sodium**	20 mg	20 mg	4.g	10%	12mg	12mg	2.40g	6 %
3	**Crospovidone**	12 mg	12mg	2.40g	6%	20mg	20mg	4g	10 %
4	**Microcrystalline Cellulose**	42.10mg	41.47mg	8.29g	20.73%	---	---	---	---
5	**Mannitol**	60mg	60 mg	12g	30%	---	---	---	---
6	**Pregelatinized Starch**	---	---	---	---	36.5mg	35.87mg	7.17g	17.93 %
7	**Sucralose**	10mg	10mg	2g	5%	15mg	15mg	3g	7.50 %
8	**Xylitol**	---	---	---	---	60mg	60mg	12g	30%
9	**Colloidal Silicon Dioxide**	3.40 mg	3.40 mg	0.68g	1.70 %	3mg	3mg	0.60g	1.50%
10	**Magnesium Stearate**	2mg	2 mg	0.40g	1 %	1.5mg	1.5mg	0.30g	0.75 %
11	**Citric Acid Anhydrous**	---	---	---	---	1.5mg	1.5mg	0.30g	0.75%
12	**Peppermint Flavor**	4mg	4mg	0.80g	2%	4mg	4mg	0.80g	2%
	Total	**200 mg**	**200 mg**	**40g**	**100 %**	**200mg**	**200mg**	**40g**	**100 %**

Formula (F3) consist of microcrystalline cellulose and hydroxy propyl methyl cellulose as diluent agent. Formula (F4) consist of lactose anhydrous and citric acid anhydrous were used as diluent.

Table 2: Ingredients Used in The Preparation of F3 and F4 Diclofenac Free Acid ODTs.

		F3				F4			
No	**Materials**	**Theoretical Amount**	**Actual Amount**	**Total Amount**	**Percentage %**	**Theoretical Amount**	**Actual Amount**	**Total Amount**	**Percentage %**
1	**Diclofenac Free Acid**	46.50mg	47.13mg	9.427g	23.57 %	46.5mg	47.13mg	9.47g	23.57%
2	**Croscarmellose Sodium**	20mg	20mg	4g	10%	25mg	25mg	5g	12.50 %
3	**Crospovidone**	14mg	14mg	2.80g	7%	12mg	12mg	2.40g	6 %
4	**Mannitol**	40mg	40mg	8g	20%	36mg	36mg	7.20g	18%
5	**Lactose Anhydrous**	---	---	---	---	55.50mg	54.87.mg	10.97g	27.43 %
6	**Hydroxy Propyl Methyl Cellulose**	54.50mg	53.87mg	10.77g	26.93 %	---	---	---	---
7	**Sucralose**	15mg	15mg	3g	7.50 %	15mg	15mg	3g	5.70 %
8	**Colloidal Silicon Dioxide**	3mg	3mg	0.60g	1.50 %	3mg	3mg	0.60g	1.50 %
9	**Magnesium Stearate**	1.50mg	1.50mg	0.30g	0.75%	1.50mg	1.50mg	0.30g	0.75 %
10	**Citric Acid Anhydrous**	1.50mg	1.50mg	0.30g	0.75 %	1.5mg	1.50mg	0.30g	0.75 %
11	**Peppermint Flavor**	4mg	4mg	0.80g	2%	4mg	4mg	0.80g	2%
	Total	**200mg**	**200mg**	**40g**	**100 %**	**200mg**	**200mg**	**40g**	**100%**

Formula (F5) consist of sodium starch glycolate was added as superdisintegrant, and citric acid. Formula (F6) consist of lactose anhydrous and povidone k30.

Table 3: Ingredients Used in The Preparation of F5 and F6 Diclofenac Free Acid ODTs.

		F5				F6			
No	**Materials**	**Theoretical Amount**	**Actual Amount**	**Total Amount**	**Percentage %**	**Theoretical Amount**	**Actual Amount**	**Total Amount**	**Percentage %**
1	**Diclofenac Free Acid**	46.50mg	47.13mg	9.43g	23.57%	46.50mg	47.13mg	9.43g	23.57%
2	**Croscarmellose Sodium**	22mg	22mg	4.40g	11%	20mg	20mg	4g	10%
3	**Crospovidone**	---	---	---	---	17mg	17mg	3.40g	8.50 %
4	**Sodium Starch Glycolate**	12mg	12mg	2.40g	6%	---	---	---	---
5	**Microcrystalline Cellulose**	69.50mg	68.87mg	13.77g	34.43 %	---	---	---	---
6	**Mannitol**	25mg	25mg	5g	12.50 %	20mg	20mg	4g	10%
7	**Lactose Anhydrous**	---	---	---	---	30mg	30mg	6g	15%
8	**Hydroxy Propyl Methyl Cellulose**	---	---	---	---	40mg	39.37mg	7.87g	19.68 %
9	**Sucralose**	15mg	15mg	3g	7.50 %	15mg	15mg	3g	7.50 %
10	**Colloidal Silicon Dioxide**	3mg	3mg	0.60g	1.50 %	3mg	3mg	0.60g	1.50 %
11	**Magnesium Stearate**	1.50mg	1.50mg	0.30g	0.75 %	1.50mg	1.50mg	0.30g	0.75 %
12	**Citric Acid Anhydrous**	1.50mg	1.50mg	0.30g	0.75 %	---	---	---	---

13	**Povidone K30**	---	---	---	---	3mg	3mg	0.60g	1.50 %
14	**Peppermint Flavor**	4mg	4mg	0.80g	2%	4mg	4mg	0.80g	2%
	Total	**200mg**	**200mg**	**40g**	**100%**	**200mg**	**200mg**	**40g**	**100 %**

Evaluation of Diclofenac Free Acid ODTs

Uniformity of Weight

Weight variation test was done with the tablets were selected randomly from each formulation and weighed individually to check for weight variation. The U.S Pharmacopoeia allows a little variation in the weight of a tablet. The following percentage deviation in weight variation is allowed.

Hardness Test

Tablets require a certain amount of strength, or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging and shipping. The hardness of the tablets was determined using Monsanto Hardness tester. It is expressed in Kg/cm^2. Three tablets were randomly picked from each formulation and the mean and standard deviation values were calculated. [10]

Friability Test

It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. It is expressed in percentage (%). Ten tablets were initially weighed (Winitial) and transferred into friabilator. The friabilator was operated at 100 rpm for 4 minutes or run up to 100 revolutions.

Uniformity of Thickness

The crown thickness of individual tablet may be measured with a vernier calliper, which permits accurate measurements and provides information on the variation between tablets. Other technique employed in production control involves placing 5 or 10 tablets in a holding tray, where their total crown thickness may be measured with a sliding caliper scale. The tablet thickness was measured using screw gauge.[10]

***In-Vitro* Disintegration Time**

The process of breakdown of a tablet into smaller particles is called as disintegration. The *in-vitro* disintegration time of a tablet was determined using disintegration test apparatus as per I.P. specifications. Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using pH 6.8 maintained at 37°±2°C as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in the pH 6.8 maintained at 37°±2°C. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded.[10]

***In-Vitro* Dissolution Studies**

In-vitro dissolution studies were performed on the press tablets prepared by direct compression method at 37±0.5°C using 6.8 phosphate buffer in USP apparatus I with the paddle speed 100 rpm. 5 ml of filtered aliquot was withdrawn at pre- determined time intervals and replaced with 5 ml of fresh 6.8 phosphate buffer solution maintained at the same temperature.[10]

RESULTS AND DISCUSSION

Table 4: Evaluation of Physiochemical Parameters of Prepared Formulations.

Test	**F1**					**F2**	**F3**	**F4**					**F5**					**F6**
Weight Variation	193.7mg					-	-	196.4mg					193.8mg					-
Disintegration Time	20 sec					3:40 min	>5min	22 sec					28 sec					>5min
Time(min)	1	2	4	6	8	-	-	1	2	4	6	8	1	2	4	6	8	-
Drug Release	45.22%	47.61%	76.32%	81.64%	100.31%	-	-	62.81%	87.19%	95.73%	98.19%	106.03%	47.61%	69.34%	74.98%	75.81%	83.02%	
Hardness(kg)	3.37					3.34	3.42	2.11					3.36					3.74
Friability (%)	0.15%					-	-	0.40%					0.40%					-
Thickness(mm)	3.51mm					-	-	3.54mm					3.53mm					-

***In-Vitro* Dissolution Studies**

Dissolution test of Diclofenac Free Acid ODTs: were applied using phosphate buffer pH 6.8 (potassium hydrogen phosphate with sodium hydroxide in present sodium lauryl sulfate 0.5%).

The rate of drug release in each formula as shown in table (5).

Table 5: Percentage of *In-Vitro* Drug Release (Diclofenac Free Acid) of Formulations F1, F4, and F5, Compared with Reference STD.

Formula No.	% Drug Release				
	1 min	2 min	4 min	6 min	8 min
F1	45.22	47.61	76.32	81.64	100.31
F4	62.81	87.19	95.73	98.19	106.03
F5	47.61	69.34	74.98	75.81	83.02
Reference STD	53.30	57.17	74.11	89.22	92.2

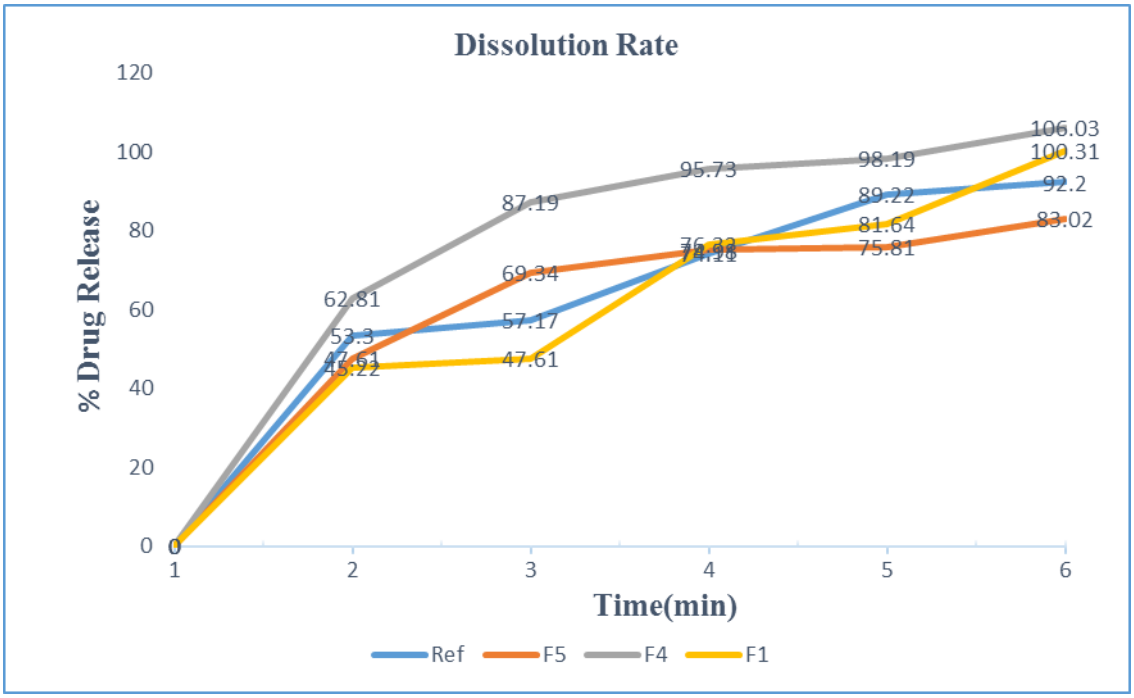

Fig. 1: *In-Vitro* Dissolution Profile of Diclofenac Free Acid Formulations F1, F4, F5 and STD.

In this study, ODT of Diclofenac free acid were prepared and evaluated for achievement of fast action of active pharmaceutical agent. The tablets were prepared by using direct compression method. Fast disintegration of tablets was achieved by using superdisintegrants in different concentrations to obtain suitable concentration of superdisintegrants which give the required approach.

Preparing Diclofenac Free Acid formulations with different percentage as disintegration agents and other excipients to overcome the taste and throat irritating properties of diclofenac sodium we use diclofenac free acid and other additives and compressed the formulation by direct compression as illustrated in tables.[1,3]

After compression of powder, the tablets were evaluated for their official test weight variation, dissolution, disintegration, and non-official tests hardness, thickness, friability.

The results shown in table,[4] hardness, thickness and friability test for all formulations F1, F4 and F5 were within the acceptable result while the disintegration time of this formulations were 20-28 seconds, due to croscarmellose and crospovidone as superdisintegrants for good disintegration, fast mouth dissolving tablets and overcome the limitations of traditional tablet dosage form.

For *in-vitro* dissolution test as illustrated in table,[5] figure.[1] the dissolution rate in formula F1 found to be 45.22%, 47.61%, 76.32%, 81.64% and 100.31% after 1, 2, 4, 6 and 8 minutes respectively. For formula F4, 62.81%, 87.19%, 95.73%, 95.73% and106.03% after 1, 2, 4, 6 and 8 minutes respectively. So, the best formulae F4 according to drug release study. While Formula F5, were found to be 47.61%, 69.34%, 74.98%, 75.81% and 83.02% after 1, 2, 4, 6 and 8 minutes respectively.

CONCLUSION

The enhancement of dissolution rate and oral bioavailability of poorly soluble drugs remains one of the most challenging aspects of drug development. In the present study were carried out on optimization of Orodispersible tablets ODTs employing novel super disintegrate by direct compression method.

Diclofenac is widely used non-steroidal anti-inflammatory drug for rheumatoid arthritis, inflammation and pain relief. Orodispersible tablets ODTs of Diclofenac Free Acid are a useful approach for pain

management and a feasible alternative to the available conventional immediate release dosage form.

Among the all formulations F4 formulation was found to be showed improved drug release characteristics. Formula F4, which consists of (Diclofenac Free Acid, mannitol, lactose anhydrous, croscarmellose sodium, crospovidone, sucralose, citric acid anhydrous, peppermint flavor powder, magnesium stearate), showed the best result in faster dissolution rates and higher efficiency values.

ACKNOWLEDGEMENT

The authors are thankful to Shephaco Pharmaceutical Industry Company-Yemen and Modern Pharmaceutical Company -Yemen for providing the research facilities for this research study.

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