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RESEARCH ARTICLE

Formulation and evaluation of tramadol and diclofenac sodium multimodal sustain release tablet dosage form

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ABSTRACT

Pain is treated using the unimodal pain management which are based on either central analgesic drug mechanism or other drug like nsaid. These drugs control the pain by central nervous system or peripheral nervous system.

But in body both system involve for the pain so for moderate to severe pain unimodal approach is not sufficient to address multimodal mechanism. But when we add peripheral anti-inflammatory drug then this multimodal drug combination provides pure pain relief for the treatment. Which prohibit ascending and descending modulation pain pathway message is inhibited by the opioid analgesics and at the site of injury where peripheral nocicepter and peripheral nerve present there NSAID require to relive the pain.

Here tramadol and diclofenac sodium tablet is preparing by wet granulation method and evaluated for various parameter like thickness of the tablet, hardness, weight variation cor uniformity, friability to solve transportation problem, drug content for evaluation. Drug release was carried out using USP type II apparatus at 80 rpm in 900ml of dissolution media for 10 hrs. Mean dissolution time is used to evaluate drug release rate from a dosage form and indicates the drug release retarding efficiency of polymer. Tramadol hydrochloride and diclofenac sodium tablet were close to first order release system.

HPMC-15 is here using for sustain release of the tablet which provide long therapeutic action of the table for 10 to12 hour Dicalcium phosphate is add as a diluents. For osteoarthritis and rheumatoid arthritis and post surgical, pain, fracture, dislocation, tooth extraction and tooth carries this tablet will vary helpful for long time action and powerfully drug action. Unlikely patient compliance will also increase because the less repetition of dose administration is required.

INTRODUCTION

Dosage forms also called unit doses are essentially pharmaceutical products in the form in which they are sprovide for use, normally involving a mixture of active drug ingredient and nondrug components, along with other non-reusable material that may not be considered either ingredient or packaging. The term unit dose can also sometimes encompass non-reusable packaging as well, although the FDA distinguishes that by solid unit-dose package. Depending on the context, multiple unit dose can for in the bulk packaging, or to a single drug product containing multiple dose or may be drug. Some dosage form sometimes refer only to the chemical formulation of a drug product's constituent drug which are called as generic product.

5 PREFORMULATION STUDY:

Preformulation study play first major role in the starting of formulation like solubility, physical characteristics like colour odour, flow property using angle of repose, and density of the all powder.

6. Experimental Work:

Manufacturing process the tablet is manufactured in number of stage these all step play an important role. Process is start from mixing by weighing, blending then granulating, drying compressing,

The materials which are use in formulation of tramadol and diclofenac tablet are as following.

Make six different formulation in which use different concentration of the diluents, polymer, glident, lubricant and etc. such formulation are evaluated by precompression and post compression parameter.

Which provide the release of the drug.

Table 6.1: Material

Sr no.	Name of ingredient						
		FTD1	FTD2	FTD3	FTD4	FTD5	FTD6
1	Diclofenac s0dium	100	100	100	100	100	100
2	Tramadol	100	100	100	100	100	100
3	HPMC K 4M	130	160	-	-	-	-
4	HPMC K 15 M	-	-	130	160	-	-
5	HPMC K100 M	-	-	-	-	130	160
6	Dicalcium phosphate	60	40	60	40	60	40
7	Magnesium stearate	2	2	2	2	2	2
8	Talc	2	2	2	2	2	2
9	PVP-30	7%					

Weighing and Dispensing:

The weight room is the entry point to manufacturing unit and a transition point for materials coming from the warehouse and entering process areas, In every entery Careful attention to design, layout and operation are essential for them

Preparation of granule:

Following particle size reduction and blending, the formulation may be granulated, which provides homogeneity of drug distribution in blend.

That is for proper mixing. This process also is very important and needs experience to attain proper quality of granule before tableting, quality of granule determines the smooth and trouble free process of tablets manufacturing. If granulation is not done in a proper manner, the resulting mixture may damage the tableting press.

Granules are agglomerates of powdered materials prepared into larger, free flowing particles. They typically fall within the range of 850 µm (No. 20 sieve) to 4.75 mm (No. 4 sieve) size. The shape of granules is gener-ally irregular.

GRANULATION METHODS:

Wet Granulation:

In wet granulation, a liquid binder or an adhesive is first added to the powder mixture. The wetted mass is then passed through a screen of the desired mesh size, and resulting granules are dried. The dried granules can be passed through a second screen ofa smaller mesh to reduce the size of the granules even further. Overwetting usually results in granules that are too hard for proper tableting, while underwetting usuallyresults in the preparation of tablets that are too soft and tend to crumble. Binding agents commonly used in wet granulation are a 10–20% aque-ous solution of corn starch, molasses, various polysaccharides (e.g., acacia gum), cellulose derivatives (such as methylcellulose, carboxymethylcellulose, and microcrystalline cellulose), gelatins, and povidone (polyvinylpyrrolidone, PVP).

6.4 DRYING PROCESS: granules are dried at 60 degree centigrade temp in the hot air oven.

Evaluation of granule:

Granules (100 mg) with diameters in the 425–1000 µm range were dissolved in 200 ml of distilled water, and the drug content of the granules was determined by UV spectroscopy at 243 nm (UVmini-1240, Shimadzu Co.

Granules ready for compression prepared by wet granulation method were evaluated for flow properties like Bulk density, Tapped density, Carr's index and Hausner's ratio. The angle of repose was measured by using funnel method, which indicates the flow ability of the granules. Loose bulk density (LBD) and tapped bulk density (TBD) were measured using the formula: LBD= weight of the powder **/**volume of the packing. TBD= weight of the powder / tapped volume granule.

Table 2:

S. No.	Bulk Density (gm/ml)	Angle of Repose (θ)	Carr's index (%)	Hausner's Ratio
1	0.38	26.40	11.80	1.16
2	0.40	28.12	15.55	1.11
3	0.41	27.49	12.20	1.14
4	0.42	29.10	14.37	1.13
5	0.39	32.44	13.21	1.15

Weighing of granule:

After the evaluation of granules weigh to it to find out total amount of the granules.

Estimation of tablet weight:

After weighing the granule find that how much amount of granule have accurate dose of tramadol and diclofenac sodium. Then total wt of granule is divided by this signal nom of tablet weight. Which provide accurate dose of the drug.

Tablet punching:

6.5.2 Common stages occurring during compression

Stage 1: first of all top punch is withdrawn from the die by the upper cam and Bottom punch is low in the die so powder falls in through the hole and fills the die from granules.

Stage 2: then bottom punch moves up to adjust the powder weight-it raises and expels some powder from the hooper.

Stage 3: After then Top punch is driven into the die by upper cam Bottom punch is raised by lower cam Both punch heads pass between heavy rollers to compress the powder granule.

Stage 4: Top punch is withdraw by the upper cam Lower punch is pushed up and expels the tablet. Then tablet is a utomaticallyremoved from the die surface by surface plate of the machine.

Stage 5: same procedure for alltablet punching.

Evaluation of tablet:

Measurement of mechanical properties is not covered pharmacopoeial procedure. Because there are also a number of tests which are frequently applied to tablets for which there are no pharmacopoeial requirement but will form a part of a manufacturer's own product specification.

General appearance:

Because "Elegance is very essential for customer acceptance so following test required and Tablet order or taste are also tested for uncoated tablet for patient compliance.

Tablet size

Size and shape is measure by micrometer Other technique is that 5 to 10 tablet holding tray where total crown thickness measure with the help of slider caliper scale this process is more rapid

Tablet thickness

The tablet which are very thick may be affect packaging particularly into blisters.

Tablet thickness is considering ±5% of standard value.

6.7.1.2 Unique identification marking

Product identification section of the current physician desk reference (PDR) PROVIDE QUICK REFERENCE to multitude of marking variation In marketing tablet include company name or symbol Product code such as national code (NDE)

Hardness:

Hardness tests/ crushing strength It is found using following method-

A. Pfizer tester
B. Strong cabb testetr
C. Schleuniger tester

The test measures crushing strength property defined as the compressional force applied diametrically to a tablet which just fractures or breake it. Among a large number of measuring devices are available. The most favored ones are Monsanto tester, Pfizer tester, and Strong cobb hardness tester. These instrument use as per the choice of user and dependind on dosage. So, strain rate depends on the operator. Heberlein Schleuniger, Erweka, Casburt hardness testers are motor driven.

Friability:

Friability (Official in USP)

The tablet may well be subjected to a rolling motion. Which is solve the problem of transportation For example, speed of friability is maintain at 25 rpm for 4 minute

Roche friabilator is most frequently used for this purpose. In the laboratory friability taster mostly Roche friabiliater is use for testing.

All the formulation tested in this apparatus data are as follow-

Table 3:

Parameter	Observation
Speed	25rpm
Dropping tablet	6 inch
Wt loss allowed	0.5 to 1% allowed

Rough handling testing

It is use for how well a tablet will hold up in its specific package and shipping container during shipment test are the-

- Vibration test
- Dropo test
- Incline plane impact test

Weight variation:

Difference between the tablet is find out using this test In this test 10tablet are use but in USP method 20 tablet

are use Process is following Weight all 20 tablets and find out the average weight then subtract the actual weight from this to find the tablet difference. Tablet will be passed if 2 or less than 2 tablet are outside the percentage limit and no tablet differ by more than 2 time the percentage limit

If the drug contain 90 to 95 active ingredient the weight variation is satisfactory

Following percentage are allowed in weight variation according to USP

Table 3:

Average wt of tablet (in mg)	Maximum tablet % allowed
130 or less	10%
130 to 324	7.5%
More then 324	5%

Post compression parameter of tramadol and Diclofenac sodium tablet:

Formulation	Hardness (Kg/cm2)	Thickness in mm	Percentage Friability	Tab Weight variation
1	4.4	2.7	0..74	Pass
2	4.2	2.8	0.80	Pass
3	4.3	2.7	0.82	Pass
4	4.6	2.7	0.81	Pass
5	4.2	2.6	0.76	Pass
6	4.5	2.7	0.79	Pass
7	4.3	2.8	0.84	Pass
8	4.4	2.6	0.81	Pass

Percentage drug content/dissolution test:

Tablet was tested in USP dissolution basket 2 in which 900 ml oh 6.4 Ph buffer solution and maintain the speed of the apparatus is 85 rpm.

Sample was widrown in every 1 hour for 10 hour test have been completed till that in every hr sample find the absorbance of diclofenac sodium and tramadol hydrochloride

• USP Dissolution Apparatus 1 - Basket (37°C)

• USP Dissolution Apparatus 2 - Paddle (37°C)

• USP Dissolution Apparatus 3 - Reciprocating Cylinder apparatus. (37°C)

• USP Dissolution Apparatus 4 - (37°C) USP Dissolution Apparatus 2 is the most widely used apparatus among these four.

7.2.3 *In-Vitro* drug release:

The *in- vitro* drug release data are mention in following table no 7.14

Table 7.15: Drug release and drug content data (FTD1 to FTD3)

Formulation	Tramadol		Diclofenac sodium	
	%CDR (10hr)±SD	Drug content±SD	%CDR (10hr)±SD	Drug content±SD
FTD1	81.59±1.11	96.3±1.94	81.23±1.22	96.5±1.09
FTD2	69.78±1.15	95.2±1.49	69.34±0.80	95.7±1.38
FTD3	97.49±0.95	99.5±0.75	96.87±1.14	98.8±0.89
FTD4	75.84±1.21	95.8±1.83	75.90±0.93	96.1±1.68
FTD5	93.43±1.12	98.9±0.58	94.27±1.27	98.3±0.95
FTD6	90.37±1.00	98.3±1.46	88.72±1.07	97.6±1.28

For preparation of sustain relelease tablet as per above show 6 batch for the formulation of sustain release tablet done. In this formulation tramadol and diclofenac both drug dose is take 100 mg per tablet. After them take different concentration of the dilunt dicalcium phosphate and magnesium stearate 2mg common and different concentration of the hpmc at different grade like HPMC k 4M, HPMC k 15 M, HPMC K 100M at 160 and 130 mg per tablet then formulated the dosage form and study precompressiom and post compression parameter .then the percentage grug contant is find.take sample in dissolution test .Take different 10 different interval per hour.and find out the % drug conc of all batch bach no FTD3 give best result from these sample.

Mathematical model:

The results obtained for in vitro drug release studies were plotted adopting four different mathematical models of data treatment as follows:

1 Zero-order model:

To study the release kinetics, data obtained from in vitro drug release studies were plotted as cumulative amount of drug released versus time.

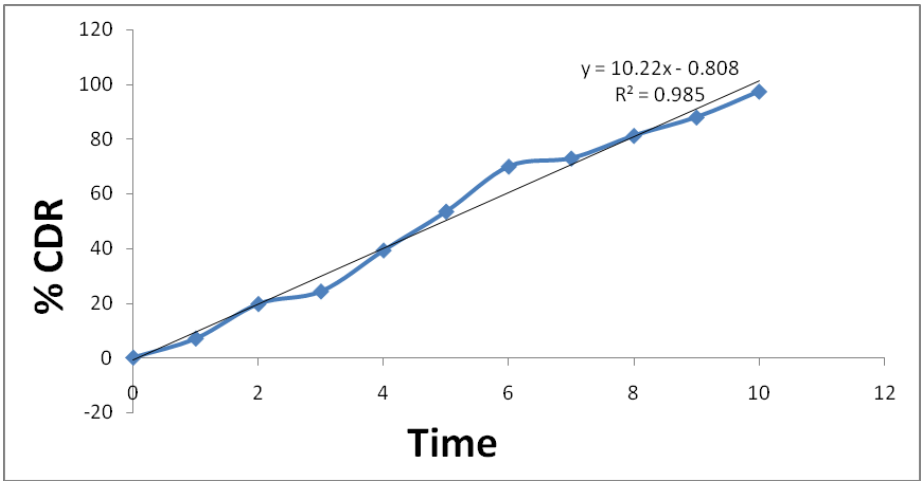

Figure 7.10: %CDR Vs Time of FDT3

7.3.2 First order model:

The data obtained are plotted as log cumulative percentage of drug remaining vs. Time.

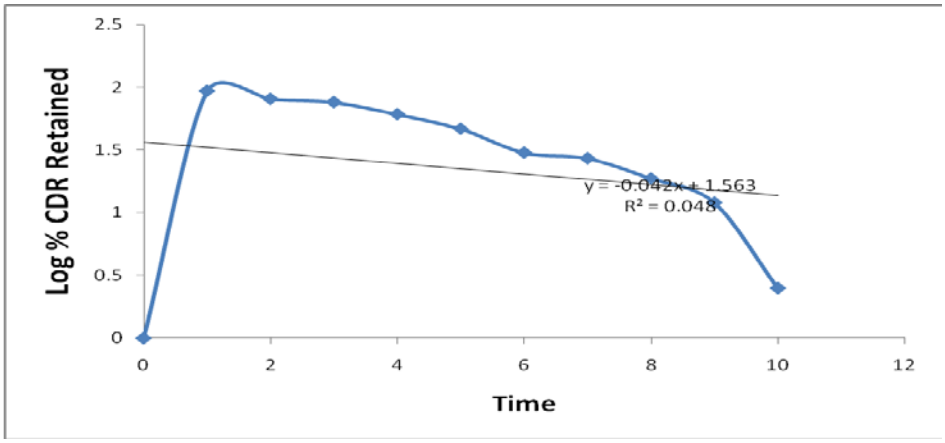

Figure 7.12: Log %CDR retained Vs Time of FDT3

Higuchi model:

Graph was plotted between cumulative percentages of drug released Vs square root of time.

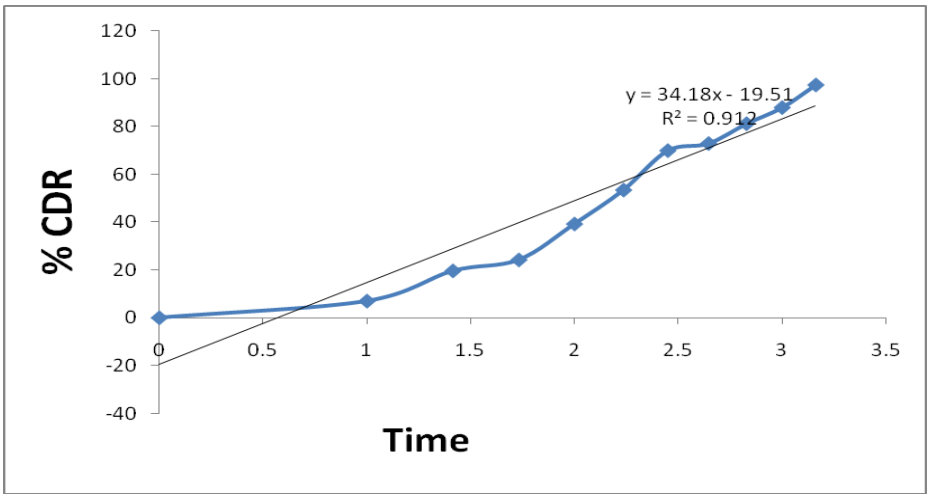

Figure 7.14: %CDR Vs SQRT of FDT3

Korsmeyer peppas model:

To study the release kinetics, data obtained from in vitro drug release studies were plotted as log cumulative percentage drug release versus log time.

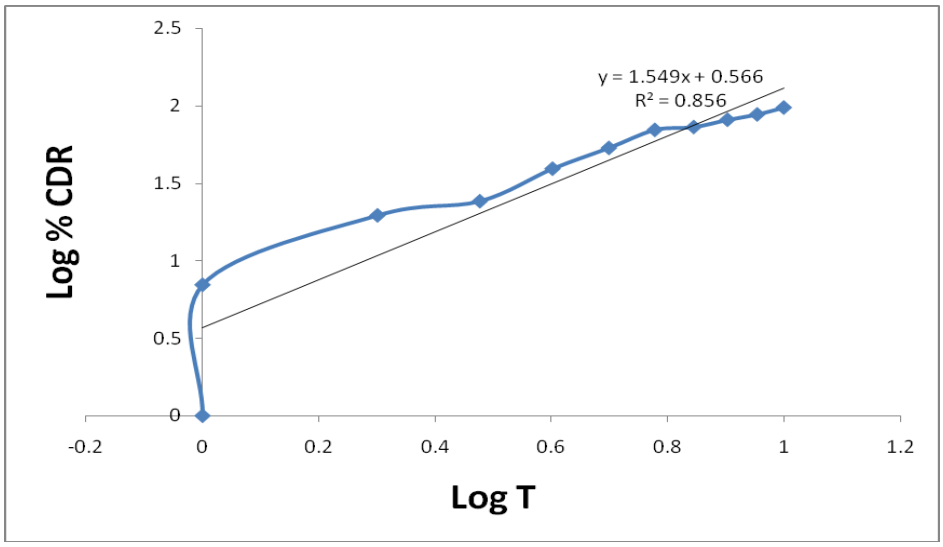

Figure 7.16: Log %CDR Vs Log T of FDT3

Table 7.16: Data of release kinetics

Form.	Zero order		First order		Higuchi		Korsmeyer peppas	
	R^2	K_0(-) (1/S)	R^2	K_1(-) M/L.S	R^2	K_H	R^2	n
FT3	0.985	10.22	0.048	0.096	0.912	30.83	0.856	0.56

After the ploting of these graph from these all six sample the batch no FDT3 follow the zero order. The drug kinetic study confirm that drug will release in sustain form .and release of drug release accordingly .the value of R^2 IS 0.985 1/S is 10.22 so which indicate the result.

7. RESULT & DISCUSSION:

RESULT:

The tramadol and diclofenac sodium sustain release tablet is successfully formulated by 6 batch of the formulation all batch are evaluated using various preformulation, precompression and post compression parameter.

The batch number Fdt3 was give the best result which formulation is stable ,well tolerated correct release of drug of tramadol and diclofenac sodium sustain release tablet is formulated and evaluated.

DISCUSSION:

Tramadol and diclofenac sodium sustain release tablet was successfully formulated using Dicalcium phosphate, with HPMC K15M for sustain release of tablet which provide long duration of action. Hence a sustain release tablet provede pure result with long time for sever and chronic pain. It is also confirm that this dosage form can be formulated for treatment of moderate to severe pain management.

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