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Full Length Research Paper

A pioneering approach to enhance Dissolution and Bioavailability of multiple drugs in a single Dosage form "speedy disintegrating tablet of Cefpodoxime Proxetil and Potassium Clavulanate"

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The demand of fast dissolving tablets has been growing during the last decade especially for geriatric and pediatric patients because of difficulties in administration. So this research was to formulation and evaluation of fast dissolving tablets with combination of two drugs namely Cefpodoxime Proxetil and Potassium Clavulanate. These tablets were prepared by using mannitol, microcrystalline cellulose etc. as filler, crospovidone, croscarmillose, SSG as super disintegrants and also used sweetener like sucralose , flavor as peppermint or orange or in combination of both, one glidant i.e. aerosil and one or combination of lubricants and antiadherents in different concentration. Total ten formations and one control batch were prepared and evaluated for hardness, friability, weight variation, content uniformity, wetting time, water absorption ratio, disintegration time and invitro drug release (all tests were performed as mentioned in The Pharmacopoeia IP,BP or USP). Optimized formulation that was DP-07 compared with control formulation for disintegration time and % drug release. The stability studies were performed as per ICH guidelines. The Optimized formulation DP-07 shown no significant variations for the tablets parameters and it was stable for the specified time period. It was concluded the FDT for Cefpodoxime Proxetil and Potassium Clavulanate can be formulated for emergency treatment of bacterial infection.

Keywords: FDT, Super Disintegrants, Stability Study, ICH.

INTRODUCTION 1-10

Oral routes of drug administration have wide acceptance around 50-60% of overall dosage forms. A lot of patients particularly children and elderly have complicatedness in swallowing tablets and capsules and as a result unable to take medicine as prescribed in such dosage form (tablet and capsule). More or less than 50% of the population is affected by such problem, resulting in the high incidence of non compliance and ineffective therapy, so the concept of fast dissolving drug delivery system emerge from the desire to provide patient with conventional mean of taking their medication. Fast Disintegrating and/ or dissolving tablets are best alternate to deliver the drug having bitter taste and Poor oral bioavailability. FDTs (Fast

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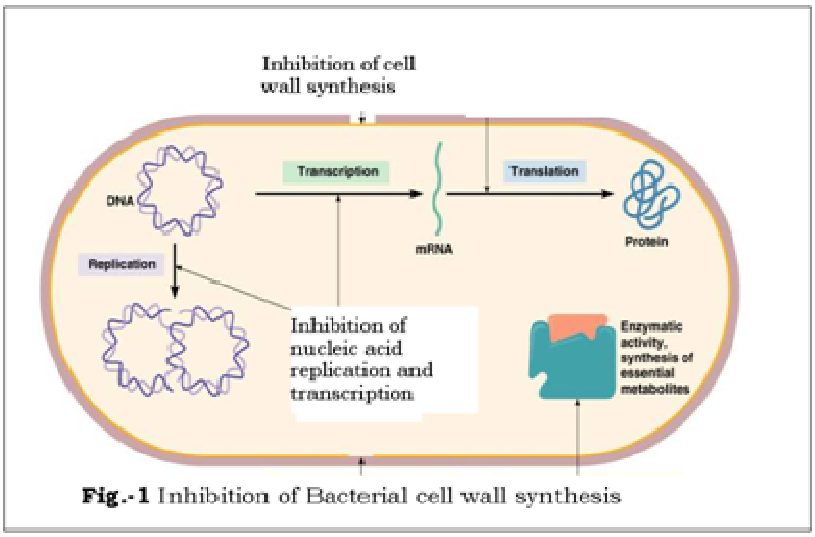

Fig.-1 Inhibition of Bacterial cell wall synthesis

Disintegrating/ Dissolving Tablets) can be manufactured by different methods as direct compression, wet granulation freeze-drying, spray drying and sublimation method. The simplicity and cost effectiveness of the direct compression process have positioned this technique as an attractive alternate to traditional granulation technologies4. Usually superdisintegrants are added to a drug formulation to facilitate the break-up or disintegration of tablet into smaller particles that can dissolve more rapidly than in absence of disintegrants The aim of this study was to formulate FDTs with sufficient mechanical integrity and to achieve faster disintegration in the small amount of water or suitable fluid or oral cavity without water.

Aim of Combination

Cefpodoxime and Potassium Clavulanate both are wide spectrum antibiotic used to treat a wide variety of infections Habib W et al. (2000). This medicated combination operates by inhibiting the reproduction of the bacteria and the production of its cell walls together (Fig.-1). This action prevents the spread of the infection and can help destroy the existing bacteria. The medication is commonly used to treat lung infections, urinary tract infections, ear infections, throat infections, and sexually transmitted diseases caused by bacteria such as Gonorrhea. Note that it will only be effective for treating bacterial infections and will not be useful for those caused by a virus or fungus [Habib W et al. 2000; Dobetti L 2003; Brown D 2003; http://www.rxlist.com/vantin-drug.htm].

Cefpodoxime Proxitel (equivalent to Cefpodoxime) [Dobetti L 2003; http://www.rxlist.com/vantin-drug.htm, http://www.rxlist.com/augmentin-chewable-tablets-drug.htm, http://www.uspbpep.com, The Indian Pharmacopoeia, Chang R-K et al. 2000; Bogner RH and Wilkosz MF 2002; US Pharmacist 2002; Humber-Droz P et al.1997; Okada M et al.2002; Pebley WS et al.1994]

Cefpodoxime proxetil is an orally administered, extended spectrum, semisynthetic antibiotic of the cephalosporin class (3rd generation oral cephalosporin). The chemical name is (RS)-1(isopropoxycarbonyloxy) ethyl (+)-(6R,7R)-7-[2-(2-amino-4-thiazolyl)-2-{(Z)methoxyimino} acetamido]-3-methoxymethyl-8-oxo-5-thia-1-azabicyclo [4.2.0]oct-2-ene-2-carboxylate. It is active against most Gram positive and Gram negative bacteria. Its empirical formula is C21H27N5O9S2. The molecular weight of cefpodoxime proxetil is 557,61. Cefpodoxime proxetil is a prodrug;, that is absorbed from the gastrointestinal tract and de-esterified to its active metabolite, cefpodoxim. Approximately 50% of the administered cefpodoxime doses absorbed systemically, over the recommended dosing range (100 to 400 mg), approximately 29 to 33% of the administered cefpodoxime dose excrete unchanged in the urine in 12 hours.

Cefpodoxime is active against a broad spectrum of Gram-positive as well as Gram-negative bacterias. Cefpodoxime is stable in the incidence of beta-lactamase enzymes. Consequently, many organisms resistant to penicillins and cephalosporins, due to their synthesis of beta-lactamase, may be susceptible to cefpodoxime. Cefpodoxime is inactivated by certain extended spectrum beta-lactamases. The bactericidal activity of cefpodoxime results from its inhibition of cell wall synthesis. The active metabolite of cefpodoxime binds preferentially to penicillin binding protein 3, which inhibits production of peptidoglycan, the primary constituent of bacterial cell walls.

Potassium Clavulanate (equivalent to Clavulanic acid [Dobetti L 2003; Pebley WS et al. 1994; Bi Y et al.1999; Bonadeo D et al. 1998; Jain RA et al. 2001; Eoga AB and

Valia KH 1999; Abdelbary G et al. 2004; Allen LV and Wang B 2001; yers GLet al. 1999]

It is a β-lactam structurally related to the penicillins and possesses the ability to inactivate a wide variety of β-lactamases by blocking the active sites of these enzymes. Clavulanic acid is particularly active against the clinically important plasmid-mediated β-lactamases frequently responsible for transferred drug resistance to penicillins and cephalosporins. Clavulanic acid, produced by the fermentation of Streptomyces Clavuligerus. Chemically, clavulanate potassium is potassium (Z)-(2R,5R)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]-heptane-2-carboxylate Clavulanate potassium molecular formula is C8H8KNO5, and the molecular weight is 237.25.

Clavulanic acid is used in conjunction with cephalosporin for the treatment of bronchitis and urinary tract, skin, and soft tissue infections caused by beta-lactamase producing organisms. Clavulanic acid competitively and irreversibly inhibits a wide variety of beta-lactamases, commonly found in microorganisms resistant to penicillins and cephalosporins. Binding and irreversibly inhibiting the beta-lactamase results in a restauration of the antimicrobial activity of beta-lactam antibiotics against lactamase-secreting-resistant bacteria. By inactivating beta-lactamase (the bacterial resistance protein), the accompanying penicillin/cephalosporin drugs may be made more potent as well. Approximately 25% to 40% of the clavulanic acid is excreted unchanged in urine during the first 6 hours after administration.

MATERIAL AND METHODS

Drugs, Cefpodoxime Proxetil and Potassium clavulanic acid along with their working stander, certificate of analysis and method of analysis were received as sample from certified manufacturer. All other excipients and chemicals used were of suitable analytical grade. This batch was prepared at WHO, GMP approved organization.

METHOD

Wet granulation, Dry granulation and direct compression methods used to prepare this combination. After so many trials we finalized direct compression method with different excipients and varied their concentration. During trail batch three superdisintegrants were used CCS, SSG and Crospovidone. The critical parameters to formulate a fast dissolving tablet are choice of superdisintegrant and optimization of concentration of superdisintegrant. The main criteria for fast dissolving tablets is to disintegrate or dissolve rapidly in oral cavity in 15-60 seconds, without need of water and should have pleasant mouth feel. The super disintegrant (Ac-Di-Sol, Crospovidone, Sodium Starch Glycolate) were used to formulate the tablets, table-1 contains all trial batch and their composition.

Flow properties of blend [http://www.rxlist.com/vantin-drug.htm; http://www.uspbpep.com; The Indian Pharmacopoeia; Bogner RH and Wilkosz MF 2002; Humber-Droz P et al.1997; Bi Y et al. 1999; Bonadeo D et al. 1998; Jain RA et al. 2001; Eoga AB and Valia KH 1999; Abdelbary G et al. 2004; Allen LV and Wang B 2001; Yers GLet al. 1999; Misra TK et al. 1999]

The flow properties of blend (before compression) were characterized in terms of angle of repose, Carr index and Hausner ratio. For determination of angle of repose (q), the blend were poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2.0 cm above hard surface. The blends were poured till the time when upper tip of the pile surface touched the lower tip of the funnel. The tan-1 of the (height of the pile/radius of its base) gave the angle of repose.

Blends were poured gently through a glass funnel into a graduated cylinder cut exactly to 10 ml mark. Excess blend was removed using a spatula and the weight of the cylinder with pellets required for filling the cylinder volume was calculated. The cylinder was then tapped as per USP monograph. Bulk density (BD) and tapped density (TD) were calculated. Hausner ratio (HR) and Carr index (IC) were calculated according to the two equations given below

$$HR = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

$$IC = 100X\ \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}}$$

Evaluation of formulated tablets [http://www.rxlist.com/vantin-drug.htm; Bogner RH and Wilkosz MF 2002; US Pharmacist 2002; Abdelbary G et al. 2004; Allen LV and Wang B 2001; Misra TK et al. 2000; Yang S et al. 2004; Heinemann H and Rothe W 1975; Roser BJ and Blair J 1998; Lee C-H et al. 2002; Lo JB 1993; Sugimoto M et al. 2001; Mizumoto T et al. 2003; Liu F-y et al. 2002; Tatara M et al. 2001]

The various formulations were evaluated for hardness, weight variation, friability, disintegration time, Invitro disintegration time, wetting time, uniformity of dispersion, drug content/content uniformity, and dissolution study.

Tablet Hardness

The strength of tablet is expressed as tensile strength (Kg/cm2). The tablet crushing load, which is the force required to break a tablet into halves by compression. It

Table1: Trial batch of disintegrating tablet of Cefpodoxime Proxetil and Potassium Clavulanate.

S.No	Name of Ingredients	Function	DP-1	DP-2	DP-3	DP-4	DP-5	DP-6	DP-7	DP-8	DP-9	DP-10
1	Cefpodoxime proxetil	API	200.0	200.0	200.0	200.0	200.0	200.0	200.0	200.0	200.0	200.0
2	Potassium clavulanic acid	API	125.0	125.0	125.0	125.0	125.0	125.0	125.0	125.0	125.0	125.0
3	Lactose monohydrate	Diluent		233.0	224.0	100.0				50.0		53.0
4	Lactose dc grade	Diluent	197.0			50.0	150.0		50.0		250.0	100.0
5	Microcrystalline cellulose 102	Dilents/ Disintegrent		20.0	20.0	47.0	93.0		213.0	150.0		90.0
6	Sodium lauryl sulphate	Surface active agent	3.0	2.0	1.5	2.0	3.0	5.0	5.0	3.0	4.0	3.0
7	Mannitol (perlitol)	Diluent	50.0		2.5	50.0		245.0		60.0		
8	Hypromellose	Binder				3.0		5.0				
9	Ethylcellulose	Binder								2.0		
10	Sodium Starch Glycolate	Super disintegrent	10.0	15.0	10.0	12.0	10.0	20.0	20.0	17.0	16.0	20.0
11	Crosspovidone	Super disintegrent	20.0	7.0			20.0	10.0	10.0			10.0
12	Croscarmellose sodium	Super disintegrent			20.0	10.0				12.0	10.0	
13	Sucralose	Sweetener	20.0	18.0	15.0	15.0	18.0	25.0	15.0	12.0	15.0	18.0
14	Pippermint Powder	Flavor	6.0	16.0	10.0		18.0	10.0	7.0	4.0		18.0
15	Orange Flavor	Flavor	2.0		10.0	18.0				4.0	18.0	
16	Magnesium stearate (e572)	Lubricant	6.0	6.0	5.0	6.0	6.0	2.5	2.5	6.0	6.0	6.0
17	Aerosil	Glident	6.0	5.0	2.0	6.0	5.0	2.5	2.5	5.0	6.0	5.0
18	Talc	Lubricant	5.0	3.0			2.0					2.0
19	Titanium dioxide	Antiadherent			5.0	6.0				5.0	6.0	
Total Weight of Tablet (mg)			**650.0**	**650.0**	**650.0**	**650.0**	**650.0**	**650.0**	**650.0**	**650.0**	**650.0**	**650.0**

Table 2: Evaluation of Lubricated Granules.

Evaluation of Lubricated Granules	
Tests	Result
LOD at 105^0C for 3 min.	2.05
Bulk Density	0.424
Tapped Density	0.625
Carr's Index	32.20%
Housenr Ratio	1.475
Flow	Poor

Table-3 Compression parameters

Punch Size-	12 mm	Flat
Lower Punch		Flat
Upper Punch		Flat
Die		Round
Tablet weight	650±3.0%	
Machine Used	Tooling B	27 stations
Speed of Machine		Normal
Humidity	20.0%	

was measured using a tablet hardness tester (Pfizer Hardness Tester).

Weight Variation Test

As per USP monograph-2091:- Weight variation test is done by weighing 20 tablets individually; calculating the average weight and comparing the individual tablet weight to the average.

Friability-USP monograph 1216

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for the Purpose. This device subjects a number of tablets (according to USP monograph 1216- tablets with a unit weight equal to or less than 650 mg, take a sample of whole tablets corresponding as near as possible to 6.5 g. For tablets with a unit weight of more than 650 mg, take a sample of 10 whole tablets) to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at a distance of 6 inches with each revolution. Reweighed sample of tablets was placed in the friabilator, which was then operated for 100 revolutions. Tablets were dusted and reweighed. Compressed tablets should not loose more than 1% of their weigh.

$$\% \text{ Friability} = 100\ X\ \frac{Loss\ Weight}{Initial\ Weight}$$

Disintegration Time

As per IP monograph 2.5.1 The disintegration time of tablet was measured in water at 240 to 260 C temp for 3 min in USP disintegration test apparatus.

Wetting Time

The method reported by Yunixia et.al. was followed to measure tablet-wetting time. A piece of tissue paper folded twice was placed in a small Petri dish (ID6.5cm) containing 6ml of pH6.8 (simulated saliva fluid). A tablet was put on the paper and the time for complete wetting was measured. Three trials for each were performed.

Wetting Volume

The tablet was placed in the center of the Petri dish and with the help of 5 ml pipette; distilled water was added drop wise on the tablet. The volume required to completely disintegrate the tablet was noted as the

Water Absorption Ratio

A piece of tissue paper folded twice was placed in a small Petri dish (10 cm diameter) containing 6 ml of water. A tablet was put on the tissue paper and allowed to wet completely. The wetted tablet was then reweighed. Water

Table 4: Evaluation of Dispersible Tablets

Evaluation of Dispersible Tablets							
No of Tablets	**Weight (mg)**	**Hardness (kg/cm2)**	**Thickness (mm)**	**Dimension (mm)**	**Disintegration time (min)**	**Friability (%)- 25 rpm for 4 mints.**	
1	652.20	4.00	5.20	12.01	0.55	25 rpm	Results
2	648.50	5.00	5.18	12.05	0.56	Revolutions	
3	650.10	3.50	5.20	12.00	0.57	100	0.31%
4	650.00	3.00	5.21	12.10	1.05	200	0.47%
5	647.90	3.50	5.20	12.00	1.06	300	0.59%
6	652.10	3.50	5.50	12.00	1.09		
7	655.20	4.50	5.21	12.00	0.57		
8	650.90	4.50	5.19	12.00	0.59		
9	655.90	5.00	5.19	12.01	1.00		
10	650.20	4.50	5.00	12.05	1.00		
11	642.90	5.00	5.20	12.05	1.06		
12	650.80	5.00	5.30	12.00	1.10		
13	652.50	5.00	5.21	12.06	0.44		
14	650.10	4.50	5.21	12.04	0.57		
15	651.00	4.00	5.21	12.05	1.05		
16	650.00	4.00	5.20	12.04	1.06		
17	652.80	5.50	5.18	12.00	1.09		
18	650.00	4.50	5.19	12.00	1.15		
19	650.00	5.50	5.20	12.05	1.20		
20	650.00	4.50	5.15	12.05	1.15		
Max	**655.90**	**5.50**	**5.50**	**12.10**	**1.20**		
Min	**642.90**	**3.00**	**5.00**	**12.00**	**0.40**		
Average	**650.70**	**4.40**	**5.20**	**12.00**	**0.90**		

Table 5: Time vs. Drug Release

Time (mints)	%Rrelease Cefpodoxime	%Rrelease Clavulanic Acid
0.0	0.0	0.00
2.0	32.5	33.80
4.0	56.2	49.56
6.0	69.1	61.87
8.0	85.0	70.14
10.0	92.1	83.25
12.0	99.0	97.80
14.0	100.1	103.50
15.0	101.0	102.26

absorption ratio, R was determined using following equation-

$$100X \frac{Wa-Wb}{Wb}$$

Where, Wa = weight of tablet after water absorption and Wb = weight of tablet before water absorption.

Uniformity of Dispersion- as mentioned in IP

Two tablets were placed in 100 ml of water and stirred gently until completely dispersed. A smooth dispersion was obtained which passes through a sieve screen with a nominal mesh aperture of 710 µm (sieve number 22).

In-vitro drug release

Tatara M et al. 2001; Lagoviyer Y et al. 2002; Wehling F and Schuehle S 1996; Wehling Fet al. 1993; Amborn J and Tiger V 2001; Khankari RK et al. 2000; Mizumoto T et al. 1996. Release of drug in vitro, was determined by

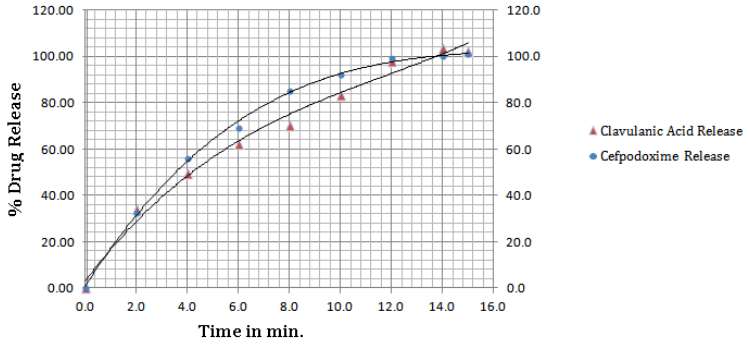

Fig.-2 Time Vs. % Drug Release from (DP-07) formulated dosage form.

estimating the dissolution profile. This is test was performed by our ADL team and finally receives data of % drug release from dosage form. Fig. 2 and tablet-5 surmised all these data's.

Stability Studies

www.ich.org/products/guidelines.html; Lagoviyer Y et al. 2002; Wehling F and Schuehle S 1996; Wehling Fet al. 1993; Amborn J and Tiger V 2001; Khankari RK et al. 2000; Mizumoto T et al. 1996; Cousin G et al. 1995; Ohta M et al. 1997; Hayakawa E et al. 1999; Milovac J et al. 1991.The stability studies of formulated tablets were carried out at 400C and 75% RH using stability chamber for three months. The effects of temperature and time on the physical characteristics of the tablet were evaluated for assessing the stability of the prepared formulations. The different parameters that were studied are disintegration time, hardness, friability, and drug content and dissolution rate.

Stability studies of fast dissolving tablets of optimized batch (DP-07)

It is the responsibility of manufacturers to see that the medicine reaches the consumer in an active form. So the stability of pharmaceuticals is an important criterion. Stability of medicinal products may be defined as the capability of a particular formulation in a specific container to remain within its physical, chemical, microbial, therapeutic and toxicological specification, i.e. stability of drug is its ability to resists detoriation.90% of labeled potency is generally recognized as the minimum acceptable potency level. Detoriation of drug may take several forms arising from changes in physical, chemical and microbiological properties. The changes may affect the therapeutic value of preparation or increase its toxicity.

Accelerated Stabilizing testing of optimized batch (DP-07)

Since the period of stability testing can be as long as two years, it is time consuming and expensive. Therefore it is essential to devise a method that will help rapid prediction of long term stability of drug.

The accelerated stability testing is defined as the validated method by which the product stability may be predicted by the storage of the product under condition that accelerates the change in defined and predictable manner.

The stability studies of formulated tablets were carried out at 400C ± 2oC / 75% RH ± 5% at room temperature for one month. The effects of temperature and time of physical characteristics of tablet were evaluated for assessing the stability of prepared formulations.

Accelerated stability studies as per ICH guidelines

The optimized formulation (DP-07) was wrapped in aluminum foils and kept in Petri dish at 40oC ± 2oC / 75% RH ± 5% in humidity chamber.

RESULTS AND CONCLUSION

In the present study it can be concluded from the characterization of fast dissolving tablets of Cefpodoxime Proxetil and potassium Clavulanic acid that formulation containing Crospovidone and Sodium Starch glycolate was most acceptable. Tablets were prepared using direct compression technique. Since the powder material was free flowing, tablets were obtained of uniform weight due of uniform die fill, with acceptable weight variations as per I.P. The average weight of the prepared tablet was found 650 mg. All the tablets were exhibit in white to offwhite colour, sweet with peppermint flavored smooth surface with zero defects. Tablet requires certain amount of

hardness to withstand the mechanical shocks in handling, packaging and at the time of application. The friability of all the formulation was found to be less than 1.0 %. The hardness of the prepared tablet varied from 3.5 to 6.5 Kg/cm2 which have satisfactory strength to withstand the mechanical shocks (Table no.4).

After 3 month accelerated Stability end product have satisfactory results. For commercialization of this product long term stability is running.

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