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Formulation and Invitro Evaluation of Enteric Coated Tablets of Penicillamine

Kola Manasa[1], Sneha Gandla[2], Gaddam Saikrishna[3], Supratim Bhunia [4], Prajwal[5], Savasani Mounika*

* Assistant Professor, Dept of Pharmaceutics, Malla Reddy Institute of Pharmaceutical Sciences, Dullapally, Near Kompally, Secunderabad, 500014, Telangana, India.

ABSTRACT

Penicillamine is a chelating agent recommended for the removal of excess copper in patients with Wilson's disease. From *in vitro* studies which indicate that one atom of copper combines with two molecules of penicillamine. Penicillamine also reduces excess cystine excretion in cystinuria. The mechanism of action of penicillamine in rheumatoid arthritis is unknown although it appears to suppress disease activity. In this present study an attempt was made to formulate and evaluate Penicillamine as enteric coated tablet. Delayed release tablets of Penicillamine were prepared by wet granulation method using HPMC and Cassava starch as polymer, Avicel PH 102 (MCC) as filler and starch as binder. The prepared tablets were evaluated for hardness, weight variation, friability and drug content uniformity and it was found that the results comply with official standards. The prepared tablets were coated using enteric coating polymer such as cellulose acetate phthalate, Eudragit L 100 by dip coating method. The *invitro* release study revealed that the prepared tablets were able to sustain the drug release into the intestine. The release kinetics studies showed that the release was first order diffusion controlled and the n values obtained from the Korsmeyer-Peppas model showed that the release mechanism was super case-II transport. Stability studies indicated that the developed tablets were stable and retained their pharmaceutical properties at room temperature and 40°C / 75% RH for a period of 1 month…

Keywords: Penicillamine, Delayed release, HPMC, Cassava starch.

BASIC INTRODUCTION:

Sustained release drug delivery systems

Dr. Paul Ehrlich's 'magic bullet' concept though realized late, offers a logical solution to the age-old problem of unrelated and unwanted effects of therapeutic agents and optimizing the drug therapy in its true sense. Although sustained/ controlled drug delivery can be considered as the progenitor of magic bullet concept in practice, the term sustained/controlled has been used with the widest possible meaning.

Probably the earliest work in the area of sustained drug delivery dosage forms can be traced to the 1938 patent of Israel Lipowski. This work involved coated pallets for prolonged release of drug and was presumably forerunner to the development of the coated particle approach to sustained drug delivery that introduced in the early 1950s.

Ideally, a drug should arrive rapidly at the site of action (receptor) in the optimum concentration, remain for the desired time, be excluded from other sites, and be rapidly removed from the site when indicated i.e., the basic goal of the therapy is to achieve a steady state blood level that is therapeutically effective and non-toxic for an extended period of time.

Generally, the time course of a dosage form (pharmacokinetics) in man is considered to be controlled by the chemical structure of the drug. Decreasing the rate of absorption and/ or changing the dosage form provide a useful adjunct. When it is feasible or desirable to modify the drug compound on a molecular level, often sought is a product that will require less frequent administration to obtain the required biologic activity time profile; for example, a tablet that has the same clinical effect when administrated every twelve hours. In another instance, it may be desirable to decrease to decrease the absorption rate in order to obtain a more acceptable clinical response.

Oral ingestion has long been the most convenient and commonly employed route of drug delivery. Indeed, for sustained release systems, oral route of administration has received

most of the attention with respect to research on physiological and drug constraints as well as design and testing of products. This is because of the fact that there is more feasibility in dosage form design for oral route than for parenteral or any other route. The design of oral sustained release delivery systems is subject to several intercalated variables of considerable importance. In conventional drug therapy, it can be seen from the Figure.1 that the administration of drug by either intravenous injection or an extravascular route e.g., orally, intramuscularly, or rectally does not maintain drug blood level

within the therapeutic range for an extended period of time. The short action is due to the inability of conventional dosage forms to control temporal delivery.

Enteric Coating :

An oral dosage form in which a tablet is coated with a material to prevent or minimize dissolution in the stomach but allow dissolution in the small intestine. This type of formulation either protects the stomach from a potentially irritating drug (e.g., aspirin) or protects the drug (e.g., erythromycin) from partial degradation in the acidic environment of the stomach.

An enteric coating is a barrier applied to oral medication that controls the location in the digestive system where it is absorbed. Enteric refers to the small intestine; therefore, enteric coatings prevent release of medication before it reaches the small intestine.

MARERIALS AND METHOD:

PREPARATION OF CALIBRATION CURVE OF PENICILLAMINE

Procedure for standard curve in pH 6.8 phosphate buffer:

- 10 mg of penicillamine was dissolved in 10 ml of pH 6.8 by slight shaking (1000 µg/ml). 1 ml of this solution was taken and made up to 10 ml with pH 6.8, which gives 100 µg/ml concentration (stock solution). From the stock solution, concentrations of 5, 10, 15, 20, 25 and 30 µg/ml in pH 6.8 were prepared.
- The absorbance of diluted solutions was measured at 216 nm and a standard plot was drawn using the data obtained.

Table 7.3. Formula for the preparation of Penicillamine tablets

Material Used	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
Penicillamine (mg)	40	40	40	**40**	40	40	40	40
HPMC (mg)	25	50	75	**100**				
Cassava starch (mg)					25	50	75	100
Avicel PH 102 (mg)	129	104	79	**54**	129	104	79	54
Starch paste 5%	qs	qs	qs	**qs**	qs	qs	qs	qs
Talc (mg)	2	2	2	**2**	2	2	2	2
Magnesium stearate (mg)	4	4	4	**4**	4	4	4	4
Total	200	200	200	**200**	200	200	200	200

Preparation of Penicillamine tablets

Preparation of granules

Penicillamine granules for tabletting were prepared by wet granulation method[42]. Specified quantity of Penicillamine, hydroxypropyl methylcellulose (HPMC), Cassava starch, and Avicel PH 102 were weighed according to the formula and transferred in a mortar and pestle and mixed thoroughly. The powder mass was mixed with 5% starch paste to obtain a sludgy mass and this was passed through sieve no 12 to obtain the granules. The granules prepared were dried at 50ºC for 4 h. The dried granules were screened through sieve no 22 & 44 and stored for further studies. The specified quantity of magnesium stearate and talc were finally added and mixed for the compression of tablets.

Preparation of Penicillamine tablets

An ideal mixture of granules was directly punched into tablets weighing about 200 mg containing 40 mg of Penicillamine sodium sesquihydrate, using rotary tablet compression machine (12 stations, Karnavati, India), using 8 mm diameter concave punches. The different batches of Penicillamine tablets were collected and stored in air tight containers.

Characterization of Penicillamine compressed tablets

Pre compression parameters

Percentage yield The prepared Penicillamine granules were completely collected and weighted. The percentage product yield was calculated from its theoretical and practical product yield.

Practical product yield

Percentage yield (%) = x 100

Theoretical product yield

RESULTS AND DISCUSSIONS

***In vitro* drug release studies**

The *in vitro* dissolution studies were carried out for the prepared tablets using USP apparatus type II. The *in vitro* release profiles of Penicillamine tablets are shown. The cumulative percentage of release of Penicillamine from the prepared tablets was varied from 64.02 ± 0.42% to 99.32 ± 0.16% depends upon the drug polymer ratio for 12 h.

Table - *In vitro* drug release profile of Penicillamine from various tablet formulations (F1 to F4)

Time (h)	Cumulative percentage of drug released			
	F1	**F2**	**F3**	**F4**
0	0	0	0	0
0.5	35.04±0.06	28.13±0.15	18.86±0.23	22.41±0.09
1	46.71±0.22	37.85±0.36	21.75±0.42	28.26±0.12
1.5	53.44±0.24	43.64±0.16	28.45±0.35	33.98±0.24
2	64.22±0.15	52.88±0.05	38.21±0.05	40.78±0.35
3	71.16±0.32	60.29±0.13	45.90±0.09	55.66±0.04
4	80.24±0.27	68.61±0.18	52.87±0.42	59.09±0.15
6	89.66±0.40	77.57±0.07	60.59±0.16	67.11±0.11
8	96.68±0.36	86.08±0.06	69.33±0.11	73.21±0.08
10		95.52±0.05	78.73±0.09	88.56±0.12
12			89.20±0.08	95.20±0.08

Discussion: The *in vitro* diffusion data of all the designed formulations are shown and dissolution profiles depicted in figures. *In vitro* drug release data of all the enteric coated formulations of Penicillamine was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetics and according to equations of drug release.

Table-*In vitro* drug release profile of Penicillamine from various tablet formulations (F5 to F8)

Time (h)	Cumulative percentage of drug released			
	F5	**F6**	**F7**	**F8**
0	0	0	0	0
0.5	17.23±0.08	10.19±0.15	28.39±0.26	14.52±0.14
1	23.15±0.12	18.23±0.11	37.48±0.15	22.38±0.19
1.5	34.04±0.42	26.94±0.24	42.12±0.11	26.32±0.24
2	41.56±0.25	35.91±0.35	54.87±0.05	38.89±0.06
3	48.52±0.16	42.13±0.41	63.94±0.23	52.64±0.01
4	56.24±0.08	48.99±0.05	70.52±0.36	62.25±0.14
6	61.51±0.14	58.63±0.16	89.19±0.04	73.46±0.32

8	74.96±0.28	62.44±0.37	88.25±0.12	76.25±0.46
10	82.12±0.27	71.03±0.42	95.32±0.16	85.15±0.32
12		78.22±0.03		90.84±0.12

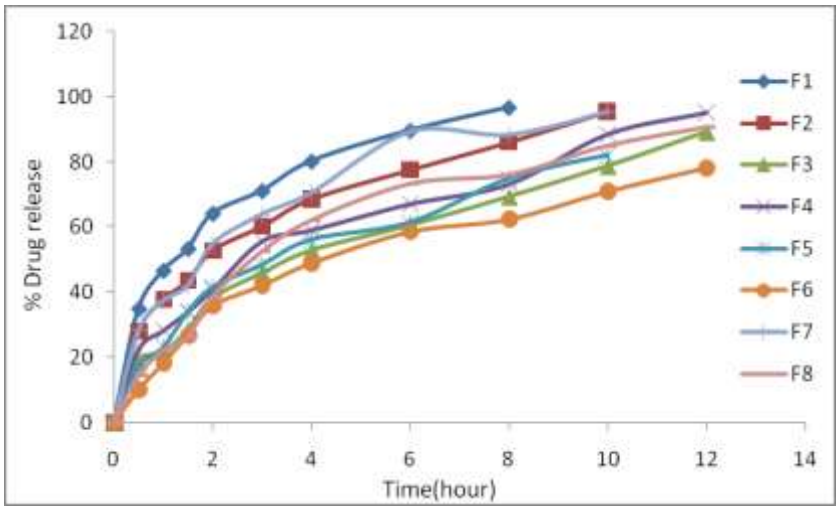

Figure: *In vitro* drug release profile of Penicillamine from various tablet formulations (F1 to

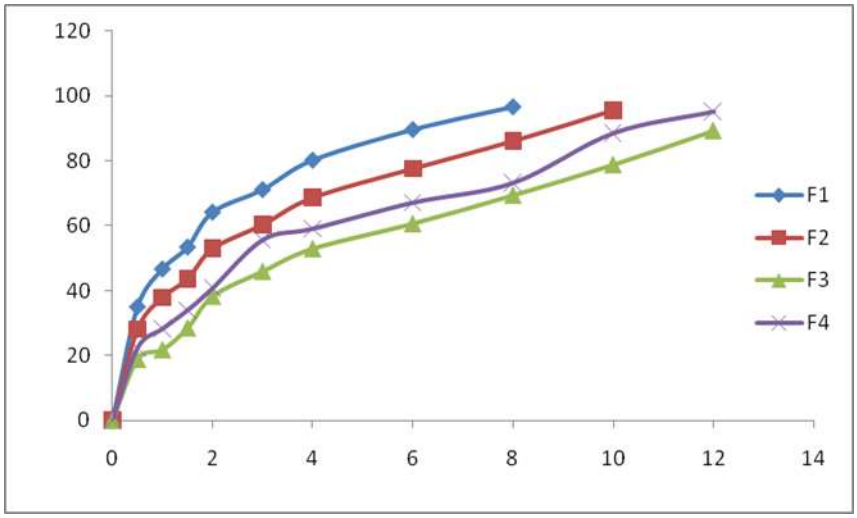

Figure: *In vitro* drug release profile of Penicillamine from various tablet formulations (F1 to F4).

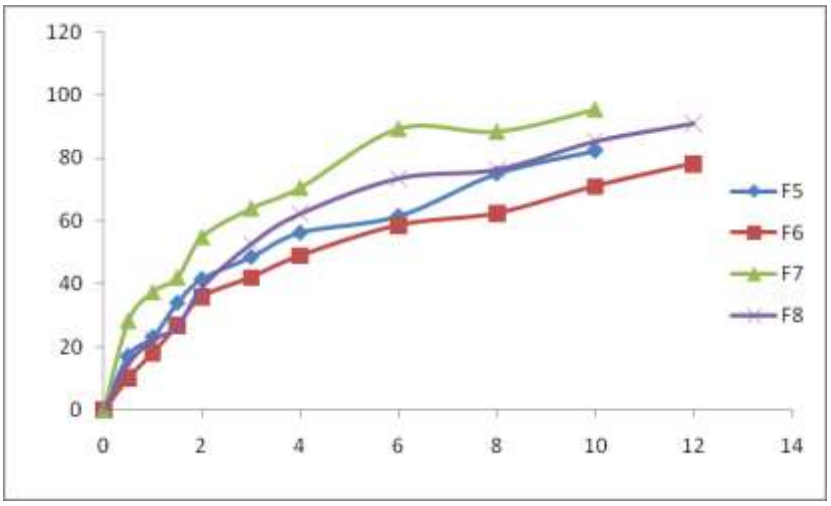

Figure: *In vitro* drug release profile of Penicillamine from various tablet formulations (F5 to F8).

Discussion:

From the above *invitro* diffusion studies we can say that from formulation F1 to F4 polymer like HPMC were used with quantity of 25, 50, 75, 100 mg. where as from formulation F5 to F8 were developed by using polymer like cassava starch instead of HPMC at a quantity of 25, 50, 75, 100 mg.By comparing with all formulation from F1 to F8 we can conclude that F4 formulation shows more maximum drug release over 12 hr time period with compare to all other formulation.

Physicochemical evaluation of coating films

Physicochemical evaluation of cellulose acetate phthalate, Eudragit L100 coating solution (films) were studied for different parameters such as film thickness, film weight and film solubility. The enteric polymer cellulose acetate phthalate, Eudragit L100 films were found to be completely soluble in pH6.8 and insoluble in pH1.2.

Table- Physicochemical evaluation of different polymer coating films

Polymer	**Parameter**			
	Film solubility		**Film thickness (mm)**	**Film weight in gm (1 cm × 1 cm)**
	pH1.2	**pH6.8**		
CAP	Insoluble	Soluble	0.39±0.07	0.103±0.06
Eudragit L 100	Insoluble	Soluble	0.38±0.08	0.100±0.03

Data of physicochemical evaluation of coated tablets.

The tablets were coated by dip coating method. The results of physicochemical evaluation of prepared coated tablets are shown in Table 5.10. The tablets were evaluated for weight variation, hardness and drug content. The weight variation was found to be between 0.210 ± 0.024 % to 0.216 ± 0.015%. The drug content was found to be between 93.65± 0.35% to 99.14 ± 0.18%. The hardness was found to be from 5.2 ± 0.11 to 6.5 ± 0.15 kg/cm^2.

Table -Physicochemical evaluations of coated Penicillamine tablets

Polymer	**Batch Code**	**Parameter**		
		Average weight * (g)	**Hardness** Kg/cm^2**	**Drug content*** (%)**
CAP	**E1F4**	0.211 ± 0.035	6.5 ± 0.15	96.75 ± 0.14
Eudragit L 100	**E2F4**	0.216 ± 0.015	6.5 ± 0.31	98.27 ± 0.45

In vitro drug release studies of enteric coated tablet

Table and Figure show the *in vitro* release profile of Penicillamine from the various enteric coated tablets.

Table - *In vitro* release of Penicillamine from CAP coated tablet and Eudragit L 100 coated tablet for the formulation of F4

pH	Time (h)	Cumulative percentage of drug released	
		E1F4	E2F4
1.2	0.5	0	0
	1	0	0
	1.5	0	0
	2	0	9.87±0.14
6.8	3	24.52±0.	27.45±0.19
	4	32.65±0.12	43.37±0.24
	6	48.74±0.18	56.16±0.17
	8	58.32±0.24	64.24±0.32
	10	65.87±0.32	72.96±0.24
	12	89.45±0.26	78.37±0.38

Figure. *In vitro* release of Penicillamine from CAP coated tablet and Eudragit L 100 coated tablet for the formulation of F4

Discussion: *In vitro* release of penicillamine was performed by F4 Formulation by taking two CAP and Eudragit L 100**,** where E1F4 shows more release time with compare with E2F4.

Release kinetics of enteric coated tablets

Data obtained from *in vitro* release studies of the CAP coated (E1F4) were fitted to various kinetic equations such as zero order, first order, Higuchi model and Korsmeyer- Peppas model and the results are presented.

Table-Release kinetics profile of formulation E1F4

Time (h)	Square root of time	Log time	CDR	%CDR	Log of %CDR	Log Cu % of drug remaining
0.5	0.707	-0.301	0	0	0	2
1	1	0	0	0	0	2
1.5	1.224	0.176	0	0	0	2
2	1.414	0.301	0	0	0	2
3	1.732	0.477	9.29	23.52	1.371	1.883
4	2	0.602	12.51	31.65	1.500	1.834
6	2.449	0.778	19.27	48.74	1.687	1.709
8	2.828	0.903	22.66	57.32	1.758	1.630
10	3.162	1	26.04	65.87	1.818	1.533
12	3.464	1.079	28.64	72.45	1.860	1.440

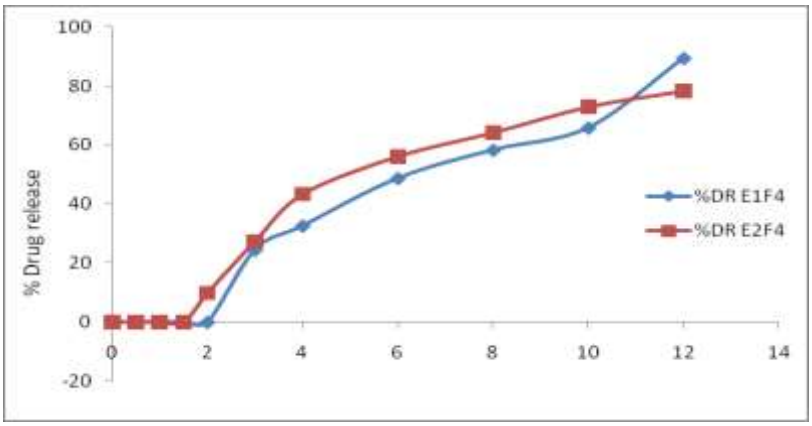

Figure: Zero order release kinetics of formulation E1F4

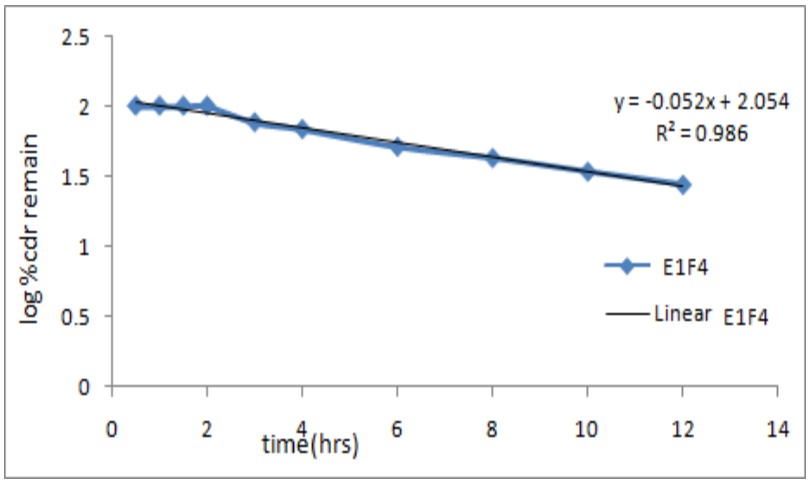

Figure: First order release kinetics of formulation E1F4

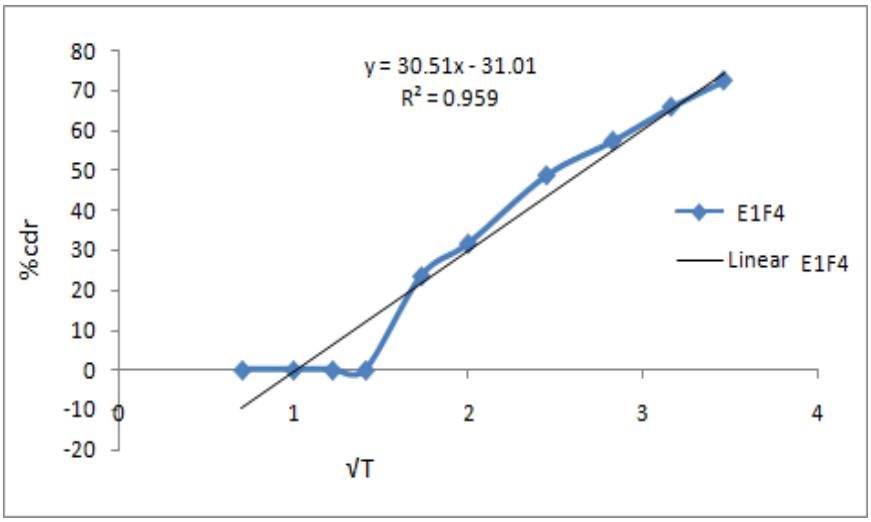

Figure: Higuchi model release kinetics of formulation E1F4

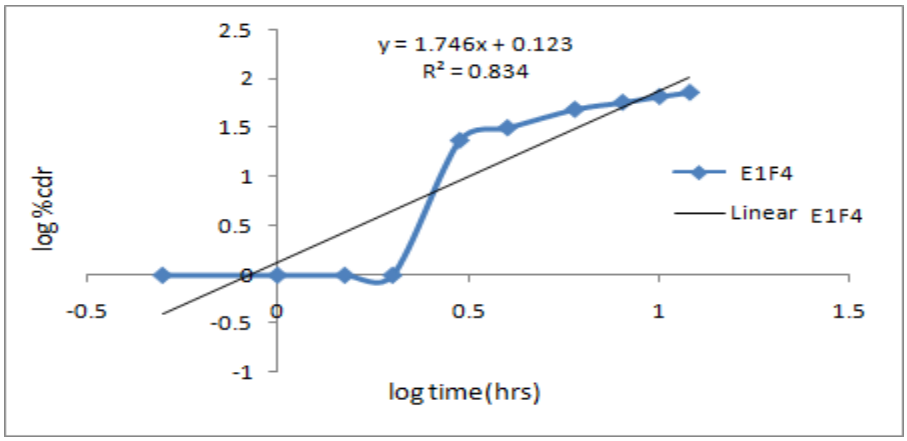

Figure: Korsmeyer-peppas model release kinetics of formulation E1F4

Stability studies of cellulose acetate phthalate coated Penicillamine tablets for F4

A study was carried out to assess the stability of the CAP coated Penicillamine tablets. Stability studies were carried out at room temperature and 40°C / 75% RH over a period of 1 month. Samples were evaluated at 0, 10, 20 and 30 days for different parameters such as physical appearance, hardness, weight variation, drug content and dissolution. The results of the stability studies are given.

Table - Stability studies of cellulose acetate phthalate coated tablet formulation E1F4

Evaluation Parameter	**Observation in Day**						
	Initial	**Room temperature**			**40± 1°C / 75% RH**		
		10	**20**	**30**	**10**	**20**	**30**
Physical Appearance	Dark red color tablets	No change	No change	No change	No change	No change	No change
Average weight of tablet (g)	0.205	0.255	0.256	0.260	0.257	0.259	0.262
Hardness kg/cm^2	6.5	6.5	6.6	6.6	6.4	6.4	6.3
Drug content* (%w/w)	100	99.54 ±0.12	99.51 ±0.08	99.42 ±0.09	99.84 ±0.13	99.47 ±0.14	99.56 ±0.10
% CDR*	87.71 ±0.14	87.31 ±0.08	87.43 ±0.15	87.08 ±0.23	87.09 ±0.35	86.78 ±0.19	86.53 ±0.45

*(n=3 ± SD), Initial Drug content as 100% w/w

CONCLUSION-

Penicillamine is a chelating agent recommended for the removal of excess copper in patients with Wilson's disease. From *in vitro* studies which indicate that one atom of copper combines with two molecules of penicillamine. Penicillamine also reduces excess cystine excretion in cystinuria. This is done, at least in part, by disulphide interchange between penicillamine and cystine, resulting in formation of penicillamine-cysteine disulphide, a substance that is much more soluble than cystine and is excreted readily. Penicillamine interferes with the formation of cross-links between tropocollagen molecules and cleaves them when newly formed. The mechanism of action of penicillamine in rheumatoid arthritis is unknown although it appears to suppress disease activity.The study led the following conclusions:

- The drug Penicillamine was selected for the study, because of its availability, proved activity and better clinical applications.
- The compatibility studies using FT-IR revealed that there was no interaction between the selected drug Penicillamine and the polymers HPMC.The Penicillamine granule were prepared by wet granulation method. The physicochemical parameters of the granules were observed that they support the ideal flow nature of the formulated granules.

The Penicillamine tablets were prepared by wet granulation method. The physicochemical evaluation of the prepared tablets was found within the standards Pharmacopeial limits.The effect of enteric coating on the *in vitro* drug release, none of the CAP enteric coated tablets showed drug release during the first 2 h in pH 1.2. While the Drug coat L100 and Eudragit L100 coated formulation showed a drug release of 0.5% to 1% during the first 2 h in pH 1.2.Release of drug from the tablets was first order diffusion controlled as indicated by higher r^2 values in First order kinetic and Higuchi model. The n value of Kors Meyer Peppa's equation indicated that the release mechanism was super case-II transport.The optimized formulation was stable and retained the pharmaceutical properties at room temperature and 40^0C / 75% RH over a period of 1 month.Based on the observations, it can be concluded that the formulated delayed release tablets of Penicillamine using widely accepted and physiologically safe polymers and other excipients was capable of exhibiting sustained release properties for a period of 12 h. The enteric coated, especially the CAP coated tablets, did not release the drug in the acidic pH 1.2 for a period of 2 h. They are thus may be reducing the dose intake, prevent the degradation of drug in acidic pH 1.2, minimize the blood level oscillations, dose related adverse effects and cost and ultimately improve the patient compliance and drug efficiency.

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