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College of Pharmacy

Formulation and Evaluation of Colon Targeted Tablets Containing Prednisolone Solid Dispersion

A Thesis

Submitted to the Department of Pharmaceutics and the Committee of Graduate Studies of the College of Pharmacy / University of Al - Mustansiriyah in Partial Fulfillment of the Requirements for the Degree of Master of Science in Pharmacy "Pharmaceutics"

By

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

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I certify that this thesis, titled ***(Formulation and Evaluation of Colon Targeted tablets containing Prednisolone Solid Dispersion)****, was prepared under my supervision at college of pharmacy/university of Al-Mustansiriyah, as a partial fulfilment of the requirements for the degree of master of science in pharmacy (Pharmaceutics).*

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Date: / / 2015

Dedication

To .....

My mother, *you are like the roots of an old tree, no one can see it, but everyone knows that it makes the tree live. You are the first person on this whole earth which understood me always; you are always my shining star. Thanks for being always when i needed you, for your endless efforts and support and all what we have reached is for your patience, endurance and prayer ... God bless you my lovely mother.*

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My children (Ula & Hamza), *you are the best thing happened to me in life. For you, I'll always be, you are the hope… God bless you my lords.*

I dedicate my thesis with love

Sura

2015

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Sura

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Abbreviation

Abbreviation	Meaning
BCS	Biopharmaceutical classification system
CTDDS	Colon targeted drug delivery system
DSC	Differential scanning calorimetry
DW	Distilled water
FTIR	Fourier transforms infrared spectroscopy
GIT	Gastrointestinal tract
NSAIDs	Non-steroidal anti-inflammatory drugs
P	probability
PEG	Poly ethylene glycol
pH	Negative logarithm of hydrogen ion concentration
PKa	Negative logarithm of dissolution constant
PVP	Polyvinylpyrolidone
PXRD	Powder x-ray diffraction
rpm	Revolutions per minute
SEM	Scanning electron microscopy
SLS	Sodium lauryl sulphate
USP	United State pharmacopeia

Abstract

The colon specific drug delivery system has provided the importance for drugs, which are especially absorbed from colon region by preventing the degradation in upper gastrointestinal tract (GIT). Drug release at this site will ensure maximum therapeutic benefits. So is convenient for treating localized colonic diseases. **Prednisolone** is a corticosteroid drug, making it useful for the treatment of a wide range of inflammatory and auto-immune conditions such as Crohn's disease, ulcerative colitis, rheumatoid arthritis and pericarditis. According to the Biopharmaceutics Classification System Prednisolone is belonging to class II drug which has low water solubility and high permeability. Solid dispersion of prednisolone in hydrophilic carrier can provide a mean of improving its poor water solubility and enhancing dissolutions and bioavailability, thus reducing dose dependent adverse effects. This study was undertaken in order to formulate colon targeted tablet of Prednisolone were prepared from different solid dispersion formulations to ensure best and complete release of the drug at the targeted region (i.e., colon). Prednisolone solid dispersions were prepared using different water soluble carriers (D-mannitol, Poly ethylene glycol (PEG4000), Poly vinyl pyrrolidone (PVP K-30) and Kollicoat IR) , non-ionic surfactants (sodium lauryl sulphate) and enteric polymer(Eudragit L100) in various compositions using solvent evaporation methods. Different variables were examined during formulation of solid dispersion such as carrier's type and ratio, using combination of surfactant and carrier. The effect of these variables on the solubility and dissolution of drug was studied. Physical mixing of drug with different carriers was prepared and compared with those of solid dispersions of the same composition. The pure drug powder, selected solid dispersion formulas and its physical mixture were characterized using different analytical techniques. The results indicated that all the tested solid dispersion formulas showed marked

improvement in the solubility and drug dissolution compared to pure Prednisolone or physical mixtures. Kollicoat IR was the most effective carrier followed by PVP K-30, while D- mannitol, Eudragit L100 and PEG4000 were the least effective. The incorporation of surfactant (e.g., SLS in SD9) significantly ($p<0.05$) improved the Prednisolone solubility (from 345.16 μg/ml in SD3 to 585.9 μg/ml) and the initial percent of drug released at the end of the first 5 minutes of dissolution time (from 72% to 83%). Generally, as the carriers' ratio increased, the solubility of Prednisolone increased linearly, while the drug release significantly increased ($p<0.05$) with increasing carrier ratio. It was found that SD18 (Prednisolone: Kollicoat IR in the ratio 1:3) was the optimum formula. The differential scanning calorimetry, infrared spectroscopy, X-ray powder diffraction, and scanning electron microscopy. These studies indicated that Prednisolone show alteration in the shape of crystal to amorphous and decrease in crystallinity which confirms the formation of solid dispersion and no chemical interactions between the drug and the carrier. The best formula from each carrier was formulated into tablet to deliver Prednisolone to the colon in a pre-solubilized form. The formulas were compressed into fast disintegrating tablets using drug compatible excipients and the best formula was coated with Eudragit S100 as a pH-responsive polymer. The effects of the type and conc. of superdisintegrants used in preparing fast disintegrating solid dispersion tablets were investigated and the coating level of Eudragit S100 on tablets was determined to adjust the duration of lag phase. The best result was given by the 16% coat level of Eudragit S100. The results of this study shows that the formula resisted pre-colonic pH values and showed an adequate lag time for the intended colonic targeting (5 h), followed by an immediate release phase in pH 7.4. The proposed coated tablets may provide a colonic delivery system for Prednisolone with improved dissolution and bioavailability.

CHAPTER ONE

INTRODUCTION

1. Introduction

1.1 Colon targeted drug delivery system:

Oral route of drug administration is preferable route, because it is patient friendly and no intervention by a health care professional is necessary to administer the drug, especially for chronic therapies when repeated administration is required [(1)]. Among the oral dosage forms tablet of various types are the most used one, because it is convenient and safe way of administration. In addition it has advantages in terms of the chemical and physical stability as well as accurate dosing of drug over liquid dosage forms [(2)].

However, the oral route of drug administration using conventional tablets cannot be used for targeting the drug to lower gastro intestinal parts due to their almost complete release at upper gastro intestinal tract (GIT), which leads to their limited availability at the lower GIT. To overcome this difficulty, new approaches of drug delivery, have been developed. Among these approaches, colon targeted drug delivery system has been extensively investigated [(1)].

From the last few decades, a great deal of research work has been devoted to the development of the site specific drug delivery system which offers several benefits over the traditional drug treatments. The principle goal of the site specific delivery is to deliver the drug to the specific organs of the body [(3)].

Targeted drug delivery into the colon is highly required for local treatment of a variety of bowel diseases such as ulcerative colitis, Crohn's disease, amebiosis, and colonic cancer [(4)]. Colonic drug delivery has gained increased importance not just for the delivery of the drugs for the

treatment of local diseases of the colon like irritable bowel syndrome and constipation but also for the systemic delivery of proteins, therapeutic peptides, anti-asthmatic drugs, anti-diabetic agents and antihypertensive drugs [5]. A colon targeted drug delivery system (CTDDS) is preferred for drugs having instability in the acidic media, low solubility and short half-life, large volume of distribution, poor absorption, and low therapeutic index. The most critical challenge in such drug delivery approaches is to protect the formulation during its passage through the stomach and about first six meters of the small intestine arriving to colon with no loss of active ingredient by preventing the dissolution and the release till it reach the colon [6].

1.1.1 Advantages of colon targeting drug delivery system :[7-9]

The following advantages can be obtained on CTDDS:

1- One of the potential advantage for CTDDS to treat disease in colon eg., inflammatory bowel disease by delivering the drug to colon, smaller size dose of drug is required.

2- By CTDDS the frequency of dose is reduced. So, lower the cost of expensive drugs.

3- By decreasing the dose and frequency as mentioned above, possibly lead to a reduced incidence of side effects and drug interactions.

4- The colon is an attractive site where poorly absorbed drug molecules may have an enhanced bioavailability, because CTDDS has a longer retention time and appears highly responsive to agents that enhance the absorption of poorly absorbed drugs.

5- Reduce gastric irritation caused by many drugs (e.g. NSAIDS).

6- By pass initial first pass metabolism.

7- Extended daytime or nighttime activity; that mean can be used to prolong the time of drug delivery and this improve patient compliance.

8- It has low hostile environment, less peptidase activity therefore, peptides, oral vaccines, insulin, growth hormones, can be given orally using CTDDS so, decrease their degradation.

1.1.2 Limitations of colon targeting drug delivery system: [9, 10]

1- The location of drug at the distal portion of the alimentary canal, the colon is difficult to access.

2- Successful delivery of drug to colon requires the drug to be in solution before it arrives in the colon, since the fluid content in the colon is lower and more viscous than in upper GIT, which is the limiting factor for poorly soluble drugs.

3- Lower surface area and relative tightness of the tight junctions in the colon can restrict drug transport across the mucosa into the systemic circulation.

1.1.3 The most useful applications of colon targeted drug delivery system: [11, 12]

The following applications show the potential advantages of CTDDS:

1- Colon is a site where local and systemic drug delivery could be achieved, local treatment of inflammatory bowel disease, for example Ulcerative colitis and Crohn's disease. Such inflammatory conditions are usually treated with glucocorticoids and sulphasalazine.

2-CTDDS can be used for drugs used to treat asthma, and arthritis to prevent early morning attacks.

3- Formulations for CTDDS are also suitable for drugs which are polar and susceptible to chemical and enzymatic degradation in the upper

GIT and highly affected by hepatic metabolism, in particular, therapeutic proteins and peptides.

4- Other serious diseases of the colon, e.g. colorectal cancer, might also be capable of being treated more effectively, if drugs were targeted to the colon.

Table (1-1) shows drugs that are used in colon associated disease condition.

Table (1-1): Drugs used in colon associated disease condition [13].

Target Sites	Disease Conditions	Symptoms	Drugs and active
Topical /Local action	Inflammatory bowel disease (Crohn's disease	Diarrhea, abdominal pain and cramping, blood in stool, ulcers, reduced appetite and weight loss	Hydrocortisone, Prednisolone, Sulfasalazine
	Ulcerative colitis	Inflammation in the rectum, rectal bleeding, rectal pain	Mesalamine, Sulfasalazine, and mercaptopurine
	Irritable bowel syndrome	Abdominal pain or cramping, a bloated feeling, flatulence, diarrhea or constipation people with IBS may also experience alternating bouts of constipation & diarrhea, mucus in stool	Dicyclomine, Hyoscine, Propantheline, Cimetropium, Alosetron,
	Colorectal cancer	A change in bowel habits, narrow stools, rectal bleeding or blood in stool, persistent abdominal discomfort, such as cramps, gas or pain, abdominal pain with a bowel movement,	5 Flourouracil, Leucovorin,and cetuximab

		unexplained weight loss	
	Diverticulitis	Formation of pouches (diverticula) on the outside of the colon due to bacterial infection	Bactrim,Flagyl, Sulfatrim,
	Antibiotic associated colitis	Overgrowth of *Clostridium difficile* and its subsequent Toxin production	clindamycin, broadspectrum penicillins (e.g., ampicillin, amoxicillin), and cephalosporins
Systemic Action	Ulcerative colitis	Ulcerative proctitis, pancolitis, fulminant colitis	Prednisolone metasulfobenzoate, tixocortol pivalate, beclomethasone

1.1.4 Anatomy and physiology of GIT:

Gastrointestinal tract has been divided in to three major parts (1) Stomach (2) Small Intestine (3) Large Intestine [14]. The large intestine extends from the distal end of the ileum to the anus. Human large intestine is about (1.5 m) long. The cecum forms the first part of the colon and leads to the right colon or the ascending colon (just under the liver) followed by the transverse colon, the descending colon, sigmoidal colon, rectum and the anal canal as shown in figure(1-1). The physical properties of the luminal content of the colon also change, from liquid in the cecum to semisolid in the distal colon [15]. The colon and rectum have an anatomic blood supply. Lymph nodes are also present with blood vessels. Activity in the colon can be divided into segmenting and propulsive movements [16].

The important functions of Large intestine (1) promotes the growth of various microorganisms by offering friendly environment

which pay a key role in digestion of proteins, carbohydrates, into their simpler form, by secreting various enzymes [17], (2) it is storage reservoir of fecal contents, (3) expulsion of the contents of the colon at an appropriate time and (4) absorption of potassium and water from the lumen. The absorptive capacity of colon is very high, each about 2000ml of fluid enters the colon through the ileocecal valve from which more than 90% of the fluid is absorbed [18].

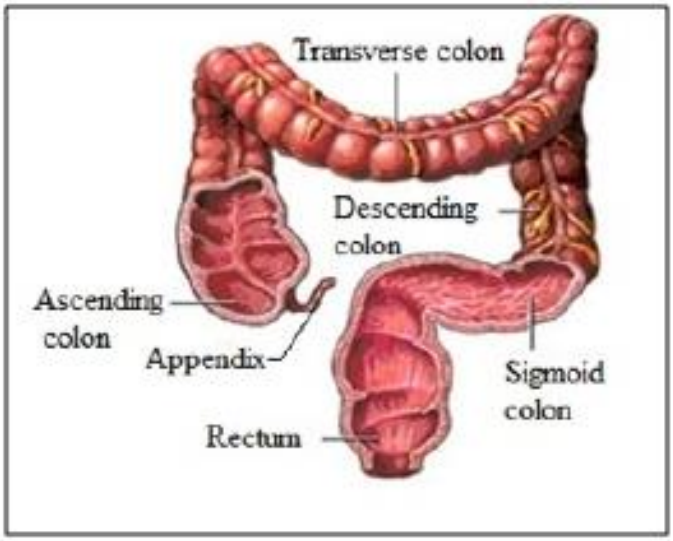


Figure (1-1): Anatomy of large intestine [19].

1.1.5 Factors to be considered in the design of CTDDS:

1.1.5.1 pH of the GIT:

The pH of the gastrointestinal tract is subject to both inter and intra subject variations. Also diet, diseased state and food intake influence the pH of the gastrointestinal fluid. The change in pH along the GIT has been used as a means for CTDDS, the table (1-2) shows pH value of different parts of GIT [20].

Table (1-2): Average pH in the GIT [21].

Sr. No.	Location	pH
1	Oral Cavity	6.2- 7.4
2	Esophagus	5.0- 6.0
3	Stomach Fasted condition Fed conditions	1.5- 2.0 3.0- 5.0
4	Small Intestine Jejunum Ileum	5.0- 6.5 6.0- 7.5
5	Large Intestine Right colon Mid colon and left colon	6.4 6.0- 7.6

1.1.5.2 Colonic microflora and enzymes:

A large number of anaerobic and aerobic bacteria are present in the entire length of the human GIT. Intestinal enzymes are used to prompt drug release in various parts of the GIT usually, these enzymes are derived from gut microflora exist in high numbers in the colon. These enzymes are used to degrade coatings or matrices as well as to break bonds between an inert carrier and an active agent (as release of a drug from a prodrug) [22]. Over 400 distinct bacterial species have been found 20-30% of which are of the genus *bacteroids* [23]. The bacterial count (colony forming unit/mL, CFU/mL) is 10^{11}-10^{12} CFU/mL in colon. Most of them are anaerobes, eg. *Bacteroides, Bificlobacterium, Eubacterium, Peptococcus, Peptostreptococcus, Ruminococcus and Clostridium*; others are facultative anaerobes eg., *E.Coli* [24]. These bacteria produce a wide spectrum of enzymes that, being reductive and hydrolytic in nature, are actively involved in many processes in the colon, such as carbohydrate and protein fermentation, bile acid and steroid transformation, metabolism of xenobiotic substances, as well as the activation and destruction of potential mutagenic metabolites. Nitroreductase, azoreductase, N-oxide

and sulfoxide reductase are the most extensively investigated reductive enzymes, while glucosidase and glucronidase are the most extensively studied hydrolytic enzymes [25].

1.1.5.3 Normal gastro intestinal transit time:

Gastric emptying of dosage forms is highly variable and depends primarily on whether the subject is fed or fasted and on the properties of the dosage form such as size and density. The arrival of an oral dosage form at the colon is determined by the rate of gastric emptying and the small intestinal transit time. Diseases affecting colonic transit time have important implications for drug delivery, in diarrhea the colonic transit time is decreased, where in constipation is increased [21]. The transit time of small dosage forms in GIT are given in table (1-3).

Table (1-3): The transit time in gastrointestinal tract under normal conditions [16]

S.No.	Main part of G.I.T	Sub part	Transit time under normal condition
1	Stomach		1-2 hr.
2	Small Intestine		3-4 hr.
3	Large Intestine		
3.1		Right (ascending + portion of transverse)	11.3 hr.
3.2		Left (descending + portion of transverse)	11.4 hr.
3.3		Sigmoid colon	12.4 hr.

1.1.5.4 Colonic absorption:

The surface area of the colon is smaller compared to small intestine and is compensated by absence of endogenous digestive enzymes and long residence time. The drug absorption in the colon occurs by the following ways:

1. Passes through colonocytes (Transcellular transport).

2. Passes between adjacent colonocytes (Para cellular transport).

Transcellular absorption involves the passage of drugs through cells by which the most lipophilic drugs pass, whereas para cellular absorption involves the transport of drug through the tight junctions between the cells and considered the route of absorption for most hydrophilic drugs [25].

1.1.6 Diseases of colon:

Inflammatory bowel diseases: Crohn's disease[6] and ulcerative colitis are two inflammatory bowel diseases that cause chronic inflammation in the GIT [26].That can treat efficiently using CTDDS.

1.1.7 Approaches to colon specific drug delivery [27- 29]

In recent years, a large number of solid formulations targeting to the lower parts of the GIT, especially the colon, have been reported. These formulations may be broadly divided into five types, which are:

1.1.7.1 pH-dependent systems:

They are pH-dependent system designed to release a drug in response to change in pH. Solid formulations for colonic delivery that are based on pH-dependent drug release mechanism are similar to conventional enteric-coated formulations but they differ in target site for delivery and the type of enteric polymers used. In contrast to conventional

enteric-coated formulations, colonic formulations designed to deliver drugs to the distal (terminal) ileum and colon, and utilize enteric polymers that have relatively higher threshold of pH for dissolution [30]. Most commonly used polymers listed in table (1-4) are derivatives of acrylic acid and cellulose.

These polymers have ability to withstand an environment pH ranging from low pH (~1.2) to neutral pH (~7.5) for several hours. Apparently, it is highly desirable for pH-dependent colonic formulations to maintain their physical and chemical integrity during passage through the stomach and small intestine and reach the large intestine where the coat should disintegrate to release the drug locally as in figure (1-2)[31].

In these systems drugs can be formulated as solid dosage forms such as tablets, capsules and pellets and coated with pH sensitive polymers as an enteric coating as Eudragit L100 and S100 are copolymers of methacrylic acid and methacrylate. For example, 5-aminosalicylic acid is commercially available as an oral dosage form coated with these copolymers [32].

Table (1-4): pH dependent Polymers [33]

Polymer	Dissolution pH
EudragitL_100	6
EudragitS_100	7
EudragitL_30D	5.6
EudragitFS_30D	6.8
EudragitL10055	5.5
Polyvinyl acetate phthalate	5
Hydroxy Propyl Methyl Cellulose Phthalate	4.5- 4.8
Hydroxy Propyl Methyl Cellulose Phthalate 50	5.2
Hydroxy Propyl Methyl Cellulose Phthalate 55	5.4

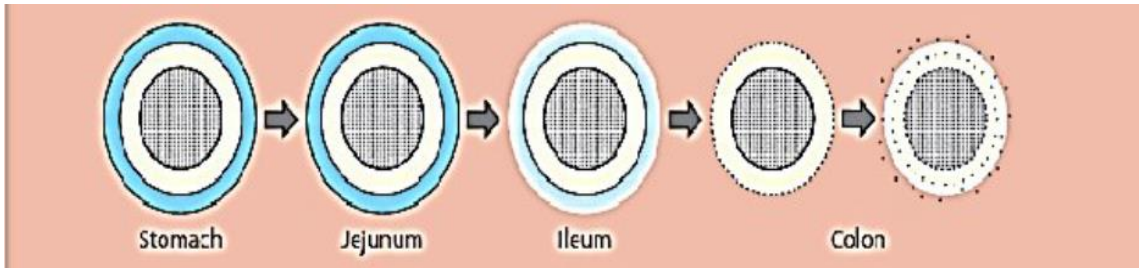


Figure (1-2): Drug release pattern of coated system at different pH conditions in GIT [34].

1.1.7.2 Time controlled (or Time-dependent) system:

Time controlled (or Time-dependent) system is designed to release a drug after a predetermined time. This system such as sustained or delayed release dosage forms are also very promising drug release systems. By this system the dosage forms may also be applicable as colon targeting dosage forms by prolonging the lag time of about 5 to 6 h [35]. However, due to potentially large variations of gastric emptying time of dosage forms in humans, in these approaches, colon arrival time of dosage forms cannot be accurately predicted, resulting in poor colonic availability [36]. Enteric coated time-release press coated tablets, are composed of three components, a drug containing in core tablet (rapid release function), the press coated swellable hydrophobic polymer layer (Hydroxy propyl cellulose layer (HPC), time release function) and an enteric coating layer (acid resistance function). The tablet does not release the drug in the stomach due to the acid resistance of the outer enteric coating layer. After gastric emptying, the enteric coating layer rapidly dissolves and the intestinal fluid begins to slowly erode the press coated polymer (HPC) layer. When the erosion reaches the core tablet, rapid drug release occurs.

The duration of lag phase is controlled by the weight of the polymer layer used for example (HPC) as in figure (1-3) [23].

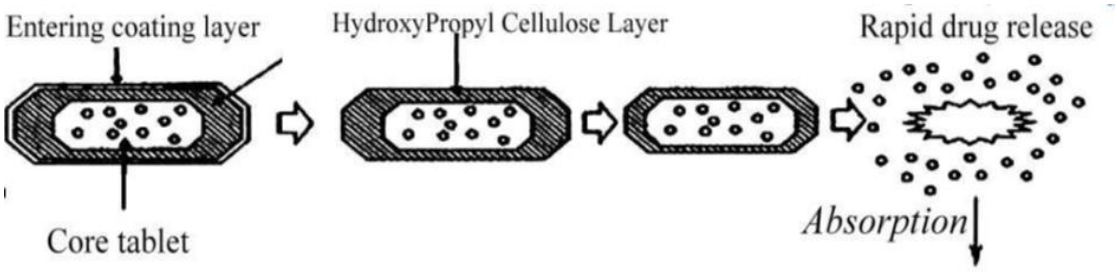


Figure (1-3): Design of enteric coated timed-release press coated tablet [23].

1.1.7.3 Microbial controlled system:

Microbial controlled system designed to release the drug by the use of abundant enterobacteria in the colon. The microflora of gut depends on fermentation of undigested materials in the small intestine for their energy requirements. The microflora performs fermentation by producing a large number of enzymes like arabinosidase, glucoronidase, galactosidase, xylosidase, nitroreductase, deaminase and urea dehydroxylase. These biodegradable enzymes are capable of degrading the polymers used for targeting the drug delivery to colon [35]. Different polymers are used for preventing the release of drug in the stomach and small intestine as listed in table (1-5). When the coated formulations reach the intestine the biodegradable polymers gets degraded by the enzymes produced by the microbial flora and the drug gets released in the targeted region [37].

Table (1-5): Different polymers used for CDDS based on Microbial drug delivery system [37]

Class	Examples
Disaccharides	Lactose, Maltose
	Cyclodextrins, Lactulose, Raffinose, Stachyose
Polysaccharides	Alginates, Amylose, Cellulose, Chitosan, Starch, Chondroitin sulphate, pectin, xanthan gum, etc.

1.1.7.4 Enzyme-based systems:

Enzyme-based systems designed to release drug as prodrug for example: azo bond conjugate, amino acid conjugate, glucuronide conjugates, etc. Prodrug is a pharmacologically inactive derivative of a parent drug molecule that requires spontaneous or enzymatic transformation *in vivo* to release the active drug [36, 38]. Covalent linkage is formed between drug and carrier, which upon oral administration reaches colon without being absorbed from upper part of GIT. In the colon, drug release is caused by high activity of certain enzymes in comparison to stomach and small intestine [24].

Different types of conjugates were used to prepare prodrugs which are succeeding in releasing the drug in colonic region [39]. They are biodegradable poly (ether-ester) azo polymers [40] [41], amino acid conjugate prodrugs[16], acrylic type polymeric prodrugs , cyclodextrin prodrugs, glucuronide conjugate[42] and others

1.1.7.5 Pressure dependent system:

Pressure dependent system designed to release the drug by using the luminal pressure of the colon. The digestive processes within the GIT involve contractile activity of the stomach and peristaltic movements for propulsion of intestinal contents [34]. The use of gastrointestinal pressure has been proposed as a method of targeting release in the distal gut [43]. Peristaltic movements of intestines along with gastric contractile activity are responsible for the propulsion of intestinal contents. These peristaltic movements establish elevated luminal pressure conditions in the colon.

The design of pressure controlled drug delivery system is based upon above mechanism. Intensity and duration of this pressure varies with the muscular contractions in the visceral organs [8, 44], the luminal pressure resulting from peristaltic motion is higher in the colon compared to pressure in the small intestine, which is attributed to the difference in the viscosity of luminal contents. In the stomach and small intestine, contents are fluidic because of plentiful water in digestive juices, but in the colon, the viscosity of the content is significantly increased due to reabsorption of water from the lumen and formation of feces. There is only one investigation related to the development of pressure controlled system for colonic delivery. This particular delivery system is in the form of a capsule, which is resistant to the pressures of the upper GIT but is collapsed in the large intestine due to increased pressure. The capsule shells are fabricated from ethylcellulose and the collapse time of the capsule in the large intestine can be controlled by adjusting the thickness of the capsule shell wall. The best thickness of the capsule wall is about 35- 60 μm [45].

1.1.8 Marketed colon specific drug delivery systems:

There are some marketed drug discovered for colon targeting listed in table (1-6)

Table (1-6): Marketed colon specific drug delivery systems [31]

Drug	Trade Name	Coating Polymers
Mesalazine	Mesazal Asacol	Eudragit® L100 Eudragit® S
Budesonide	Entrocort® Budenofalk®	Eudragit® L100-55 Eudragit® S
Sulfasalazine	Azulfidine Colo-Pleon	Cellulose acetate phthalate Eudragit® L100-55

1.2 Biopharmaceutics classification system:

The Biopharmaceutics Classification System (BCS) is a system used to differentiate the drugs on the basis of their solubility and permeability, and it is considered as guide for predicting the intestinal drug absorption provided by the U.S. Food and Drug Administration. The fundamental basis for the BCS was established by Gordon Amidon [46].

According to the BCS the drugs can be characterized into four classes depending on *in vitro* solubility and *in vivo* permeability data as represented in table (1-7). Among the four classes, class II drugs show poor solubility and high permeability. Therefore, their low ability to dissolve is a limitation to their overall rate and extent of absorption over their ability to permeate through the membrane. Hence, the formulation design for oral delivery of class II compounds should focus on the enhancement of aqueous solubility or dissolution rate. Once these drugs dissolve, they rapidly pass through biological membranes such as the GIT membrane [47].

Table (1-7): Biopharmaceutical classification system [47]

Class	Aqueous solubility	Permeability
I	High	High
II	Low	High
III	High	Low
IV	Low	Low

There are successive two processes that can be identified to describe the oral absorption of drugs from solid dosage forms: dissolution of the drug *in vivo* to produce a solution and transport of the dissolved drug across the gastrointestinal membrane. The particle size of the drug is of great importance in the transport from the GIT to the site of action by increasing the dissolution rate in the GIT [48, 49].

The techniques that are generally employed for solubilization of drug include micronization, pH adjustment, chemical modification, solid dispersion, co-solvency, complexation, micellar solubilization and hydrotropy and others [50].

The pharmacopoeia lists solubility in terms of solvent required to dissolve 1g of solute. The pharmacopoeia provides general terms to describe a given range as shown in table (1-8) [51, 52]

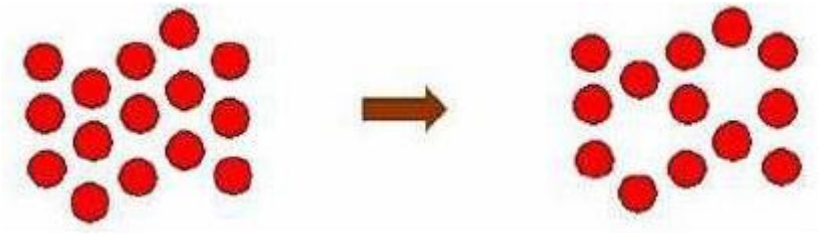
Table (1-8): USP and IP solubility criteria [51]

Descriptive term	Part of solvent required per part of solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble	10,000 and over

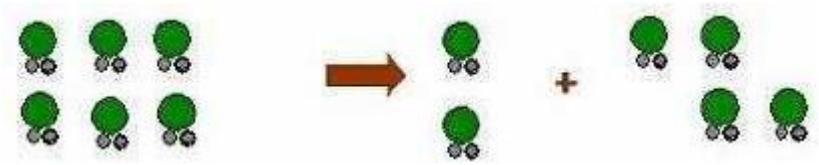
1.2.1 Process of solubilization:

The process of Solubilization involves the breaking of inter-ionic or intermolecular bonds in the solute, the separation of the molecules of the solvent to provide space in the solvent for the solute and interaction between the solvent and the solute molecule or ion are shown in the figure (1-4) [53].

Step 1: Holes opens in the solvent



Step 2: Molecules of the solid breaks away from the bulk



Step 3: The free solid molecule is integrated into the hole in the solvent

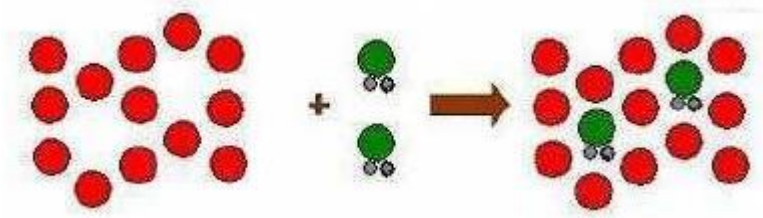


Figure (1-4): Steps of Solubilization [53]

Noyes- Whitney equation provides some suggestions as to how the dissolution rate of even very poorly soluble compounds might be improved to minimize the restrictions to oral availability [54].

$$\frac{dC}{dt} = \frac{AD(Cs - C)}{h}$$

Where, **dC/dt:** is the rate of dissolution, **A:** is the surface area available for dissolution, **D:** is the diffusion coefficient of the compound, **Cs:** is the solubility of the compound in the dissolution medium, **C:** is the concentration of drug in the medium at time **t** and **h:** is the thickness of the diffusion boundary layer adjacent to the surface of the dissolving compound. According to Noyes-Whitney equation dissolution rate can be increased by the following approaches-:

- Increasing the surface area available for dissolution by decreasing the particle size of drug.
- Optimizing the wetting characteristics of compound surface.
- Decrease the boundary layer thickness.
- Improve apparent solubility of drug under physiologically relevant conditions.

In addition administration of drug in fed state is a way to improve the dissolution rate of class II drugs [(55)].

It is frequently reported that 40% of new drug molecule in pharmaceutical industry are poorly water soluble (as reported in Pande et al., 2014) [(56)]. Therapeutic efficiency of a drug is not only depends upon the bioavailability but also on the solubility of drug molecules. Drug solubility is the highest concentration of the drug dissolved in the solvent under specific condition of temperature, pH and pressure. As solubility is an important factor in drug liberation hence it plays a key function in its bioavailability. For absorption of any drug it must be present in the form of an aqueous solution at the site of absorption. The bioavailability can be enhanced by changing in disintegration and dissolution rate of the dosage

form. Aqueous solubility smaller than 1 μg/ml will definitely create a bioavailability problem and will affect the efficacy of the drug [52].

1.2.2 Solid dispersion:

In 1961, Sekiguchi and Obi first proposed the application of solid dispersions to increase the dissolution and oral absorption of poorly water soluble drugs. They proposed the formation of a eutectic mixture of a poorly water-soluble drug with a physiologically inert, easily soluble carrier. In 1971 Chiou and Riegelman defined solid dispersion as "the dispersion of one or more active ingredients in an inert carrier matrix at solid state prepared by the melting (fusion), solvent or melting-solvent method" [57, 58].

In a recent review work by Dhirendra et al. the definition of solid dispersion was expanded and more details are given concerning the nature of carrier used and state of drug disperse in the solid dispersion "a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles". But if the drug is converted to amorphous form and exist as one phase system with polymer, it can be classified as a solid solution, whereas if the drug exists as microcrystalline dispersion and exist as two phase system, it is generally referred to as a solid dispersion [59].

1.2.3 Classification of solid dispersion:

The classification of solid dispersions according to application and recent development is summarized in figure (1-5) [60], Solid dispersions are classified by different ways on the basis of carrier used and on the basis of their solid state structure [61].

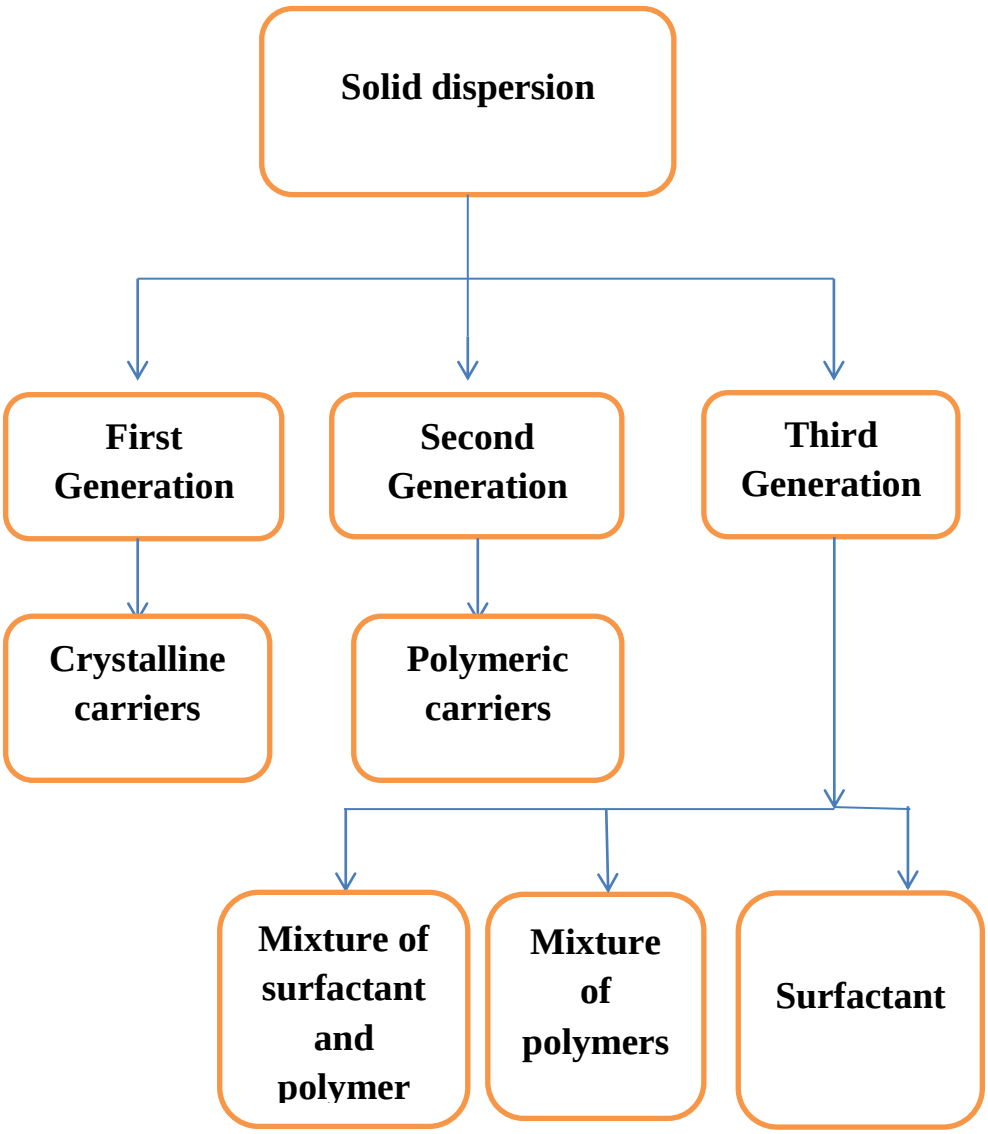


Figure (1-5): Classification of Solid dispersions according to application and recent developments [60]

1.2.3.1 Classification on the basis of carrier used:

a. First generation:

First generation solid dispersions were prepared using crystalline carriers such as sugar and urea, which were the first carriers to be employed in solid dispersion [61].

b. Second generation:

In second generation, amorphous carriers instead of crystalline carriers were used to disperse drugs which are generally polymers. Polymeric carriers can be of synthetic origin like povidone (PVP) , polyethylene glycols(PEG) and polymethacrylates whereas natural product based polymers comprises of cellulose derivatives like hydroxypropyl methylcellulose, ethyl cellulose or starch derivatives, like cyclodextrins [62 ,63].

c. Third generation:

In the third generation of solid dispersions surfactants or mixture of polymer are used as carrier. If carrier has surface active or self-emulsifying properties, the dissolution profile of poorly soluble drug can be improved and therefore result in increased bioavailability, carriers mostly used in the preparation of third generation solid dispersion (eg., Sodium lauryl Sulphate, polaxamer 407 and inulin)[56].

1.2.3.2 Classification on the basis of their solid state structure:

(A) Simple eutectic mixture:

A simple eutectic mixture of a sparingly water- soluble drug and a highly water soluble carrier can be described as a well mixed physical mixture of two crystalline components, which are completely miscible in the liquid state, but not in the solid state[64].

These components are assumed to crystallize simultaneously in very small particulate sizes. The increase in specific surface area, therefore, is mainly responsible for the increased rate of dissolution of a poorly water soluble drug [65].

(B) Solid Solutions:

According to their miscibility there are two types of solid solution:

-Continuous Solid Solutions: In a continuous solid solution, the components are miscible in all proportions. Theoretically, this means that the bonding strength between the two components is stronger than the bonding strength between the molecules of each of the individual components [66].

-Discontinuous Solid Solutions: In the case of discontinuous solid solutions, the solubility of each of the components in the other component is limited. One of the solid components is completely dissolved in the other solid component. Below a certain temperature, the mutual solubility of the two components starts to decrease [67].

According to the way in which the solvate molecules are distributed in the solvent, two types of solid solution are:

-Subsitutional solid dispersions: Substitution is possible only when the size of the solute molecules differs by less than 15% or so from that of the solvent molecules (carriers). Classical solid solutions have crystalline structure, in which the solute molecules can either substitute for solvent molecules in the crystal lattice or fit into the spaces between the solvent molecules [66].

-Interstitial solid solutions: In interstitial solid solutions, the dissolved molecules occupy the interstitial spaces between the solvent molecules (carriers) in the crystal lattice. Solute molecule diameter should be less than 0.59 times than that of solvent molecular diameter [68].

(C) Glass solution and suspension:

A glass solution is a homogenous glassy system in which solute dissolves in the glassy system. A glass suspension refers to a mixture in which precipitated particles are suspended in a glassy solvent. The term glass can be used to describe either a pure chemical or a mixture of chemicals in a glassy or transparent state. The glassy or transparent state is usually obtained by an abrupt reducing of the melt. It is characterized by transparency & brittleness below the glass transition temperature [(69)].

(D) Amorphous solid solutions:

In an amorphous solid solution, the solute molecules are dispersed molecularly but irregularly within the amorphous solvent. Carriers that were used in early studies included sugars and urea such as sucrose, dextrose and galactose. More recently, organic polymers such as polyvinylpyrrolidone (PVP), polyethylene glycol (PEG) and various cellulose derivatives have been utilized for this purpose. Polymer carriers are particularly likely to form amorphous solid solutions as the polymer itself is often present in the form of an amorphous polymer chain network. In addition, the solute molecules may serve to plasticize the polymer, leading to a reduction in its glass transition temperature [(70)].

1.2.4 Carriers for solid dispersions:

A carrier should have the following criteria to be suitable for increasing the dissolution rate of poorly soluble drugs:

1. Freely water-soluble with intrinsic rapid dissolution properties.

2. Non-toxic and inert pharmacologically.

3. Heat stable with a low melting point for the melt method.

4. Soluble in a variety of solvents and pass through a glassy state upon solvent evaporation for the solvent method.

5. Able to increase the aqueous solubility of the drug and,

6. Chemically compatible with the drug and not form a strongly bonded complex with the drug [71].

The selection of the carrier has the influence on the dissolution characteristics of the dispersed drug, since the dissolution rate of one component from the surface is affected by the other component in a multiple component mixture. Therefore, a water-soluble carrier results in a quicker release of the drug from the matrix. A poorly soluble or insoluble carrier leads to slower release of a drug from the matrix. If the active drug present is a minor component in the dispersion, faster release of a drug can be achieved from matrix. Different carriers used for preparation of solid dispersions are tabulated in table (1-9) [72]

Table (1-9): Materials used as carrier for solid dispersion [52, 72]

S.No.	Category	Carriers	Example
1	Sugars	Dextrose, sucrose, galactose, sorbitol, maltose, xylitol, mannitol, lactose	Rofecoxib from sorbitol and mannitol
2	Acids	Citric acid, succinic acid	Felodipine, rofecoxib from citric acid
3	Polymeric materials	Polyvinyl pyrrolidone(PVP), polyethylene glycol (PEG), hydroxypropyl methyl	Temazepam , felodipine, etoricoxib rofecoxib from

		cellulose (HPMC), methyl cellulose (MC), hydroxy ethyl cellulose,	PEG 4000 & 6000 and troglitazone and rofecoxib from PVP K30
4	Insoluble or enteric polymer	Hydroxy propyl methyl cellulose phthalate (HPMCP), EudragitL100, Eudragit E100, Eudragit RL, Eudragit RS	Indomethacin from eudragit E100
5	Surfactants	Polyoxyethylene stearate, poloxamer 188, deoxycholic acid, tweens, spans	Felodipin and rofecoxib from poloxamer 188
6	Miscellaneous	Pentaerythritol, pentaerythrityl tetraacetate, urea, urethane, hydroxy alkyl xanthins	Rofecoxib from urea

1.2.5 Advantages and disadvantages of solid dispersions:

Solid dispersion advantages and disadvantages are [51, 73]:

Advantages

- reduction of drug particle size, increase drug wettability
- increase solid dispersion particle porosity, porosity depends on the type of carrier, the use of linear polymers allows for a more porous particles than cross-linked

- substance in an amorphous state, more acceptable to patients than solubilization products , allow obtaining a solid oral dosage form instead of liquid form, where the substance is solubilized.

Disadvantages

- possible low stability
- changes occurring during the processing (Mechanical stress) or storage (temperature and humidity stress) leading to the crystallization of amorphous forms.
- limitations in the case of industrial scale production
- laborious and expensive methods of preparation limitations of reproducibility

1.2.6 Pharmaceutical applications of solid dispersion [74 - 77]:

Solid dispersion has many pharmaceutical applications, which can be used:

1. To increase the solubility of poorly soluble drugs by enhances the dissolution rate, absorption and bioavailability.
2. To obtain a homogeneous distribution of a small amount of drug in solid state.
3. To stabilize unstable drugs and protect against decomposition by processes such as hydrolysis, oxidation, racemization etc.
4. To dispense liquid or gaseous compounds.
5. To formulate a fast release preparing dose in a sustained release dosage form.
6. To formulate sustained release preparation of soluble drugs by dispersing the drug in poorly soluble or insoluble carrier.

7. To reduce side effects:

(a) The binding ability of drugs for example to the erythrocyte membrane is decreased by making its inclusion complex,

(b) The damage to the stomach mucous membranes by certain NSAIDs can be reduced by administration as an inclusion compound

8. To mask unpleasant taste, smell and avoid undesirable incompatibilities.

9. To convert liquid compounds into solid formulations. Liquid drugs can be manufactured as solid drug formulations such as powders, capsules or tablets e.g., unsaturated fatty acids, essential oils, nitroglycerin, benzaldehyde, prostaglandin, etc.

10. To reduce pre systemic inactivation of drugs like morphine and progesterone.

1.2.7 The mechanism by which solubility and dissolution rate enhancement occurs in solid dispersion:

1- **By particle size reduction and reduced agglomeration:**

When eutectic mixture consist of poorly water soluble drug & highly soluble carrier is exposed to water or gastro-intestinal fluid, soluble carrier dissolves leaving the drug in very fine crystalline state that will rapidly go in to solution. Due to increased surface area of insoluble compound, an enhanced dissolution rate & so increased oral absorption is obtained [78, 79].

2- By particles with improved wettability:

The enhancement of drug solubility is related to the drug wettability. It has been suggested that the presentation of particles to the

dissolution medium as physically separate entities may reduce aggregation. In addition, many of the carriers used for solid dispersions may have some wetting properties; so improved wetting may lead to reduced agglomeration and increased surface area lead to enhance dissolution rate [80].

3- By increase solubility or dissolution rate of the drug:

Many of the carriers used may increase the solubility of the drug. There appear to be two seats of observation with regard to show carrier controlled release as the rate of release is controlled by the carrier and is independent of drug properties. Secondly some system show release behavior that is dependent on the properties of the drug rather than the polymer [81].

4-By particles with higher porosity:

Particles in solid dispersions have been found to have a higher degree of porosity. The increase in porosity depends on the carrier properties; for instance, solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and, therefore, result in a higher dissolution rate. The increased porosity of solid dispersion particles also accelerates the drug release profile [82].

5- By drugs in amorphous state:

Poorly water soluble crystalline drugs, when in the amorphous state have a tendency to have higher solubility. The enhancement of drug release can usually be achieved using the drug in its amorphous state, because no energy is required to break up the crystal lattice during the dissolution process .In solid dispersions, drugs are presented as supersaturated solutions after system dissolution, if drugs precipitate it is

as a metastable polymorphic form with higher solubility than the most stable crystal form [83].

6- By soluble complex formation in microenvironment:

Organic compounds in solutions generally tend to associate with each other to some extent. Frequently, this association is too weak to be detected by standard techniques. In other cases, the intermolecular associations or complex can be readily observed and quantitated by one or more of numerous published techniques. One of more widely used methods is the solubility analysis technique. Every substance has specific, reproducible equilibrium solubility in given solvent at a given temperature.

7- By saturation of drug in microenvironment:

Another mechanism, creation of microenvironment, by hydrophilic carrier has also been reported as mean of solubility enhancement, where in a microenvironment is created where the solubility of the drug particles is increased due to high concentration of hydrophilic carrier in surrounding solution.

8- By solubilization of the hydrophobic drug in presence of the surfactant:

Solubilization using surfactant is thought to occur by benefit of the soluble dissolving in or being adsorbed onto the micelle. Thus, the ability of surfactant solutions to dissolve or solubilize water insoluble materials in solid dispersion starts at the critical micelle concentration and increases with the concentration of the micelles, this resulted in enhanced solubility of hydrophobic drug [84].

1.2.8 Methods of preparation of solid dispersions:

Numerous manufacturing methods are used for preparation of solid dispersion. The most widely used methods are fusion method and solvent evaporation method:

1.2.8.1 Melting (fusion) method:

The melting or fusion method was first suggested by Sekiguchi and Obi to prepare fast release solid dispersion dosage forms. In this method, the carrier is heated to a temperature just above its melting point and drug is incorporated in to the matrix. If the drug has high solubility in the carrier, the drug could remain "dissolved" in the solid state, yielding a solid solution. The melted mixture was then cooled and solidified rapidly in an ice bath under severe stirring. The final solid mass was crushed, pulverized and sieved. The advantages of direct melting method are its simplicity and economy. The disadvantage is that many substances either drugs or carriers may decompose or evaporate during the fusion process at high temperatures [85, 86].

1.2.8.2 Solvent evaporation method:

Tachibana and Nakamura who firstly applied solvent evaporation method for the preparation of solid dispersions. Drug (b-carotene) and carrier (PVP) were dissolved in a common solvent (chloroform) and solvent was evaporated to form the solid mass. The first step in the solvent method is the preparation of a solution containing both matrix material carrier and drug. The second step involves the removal of solvent(s) resulting in formation of a solid dispersion as shown in figure (1-6); Mixing at the molecular level is preferred, because this leads to optimal dissolution properties. Nature of the solvent used and the rate and temperature of evaporation of the solvent are the critical factors which can

affect the formed mass. The main advantage of the described solid dispersion preparation method is preventing degradation of the drug substance or carrier by preservation of low temperature needed to vaporize the organic solvent. The disadvantages include high cost of production, difficulties with selection of an easily volatile solvent and its complete removal [87- 89].

Figure (1-6): Attainment technique of solid dispersions by Evaporation method in rotatory evaporator [90].

The selection of solvent to be included for the formulation of solid dispersion should have the following properties:

1. The solvent should be a good solvent for both drug and carrier.

2. The solvent should be of low toxicity so toxic solvents should be avoided due to the risk of residual levels after preparation e.g. chloroform and dichloromethane. Ethanol can be used as alternative to these solvent as it is less toxic [91, 92].

1.2.8.3 Melting solvent method (melt evaporation):

Here the solid dispersions are prepared by dissolving the drug in a suitable liquid solvent and then incorporating the solution directly into the melt of carrier as PEG, which is then evaporated until a clear, solvent free film is left. The film is further dried to constant weight. The 5 –10% (w/w) of liquid compounds can be incorporated into polymer without significant loss of its solid property. It is possible that the selected solvent or dissolved drug may not be miscible with the melt of the polymer. Also the liquid solvent used may affect the polymorphic form of the drug, which precipitates as the solid dispersion. This technique possesses unique advantages of both the fusion and solvent evaporation methods as it is used for drugs that are unstable in melting temperature of carrier so the method solves this difficulty. From a practical standpoint, it is only limited to drugs with a low therapeutic dose e.g. below 50 mg [(93)].

1.2.8.4 Solvent deposition/evaporation:

In this technique drug is dissolved in a suitable solvent like methylene chloride form a clear solution. The carrier is then dispersed in the resultant solution by constant stirring and the solvent is evaporated under the controlled temperature and pressure. The resultant mass is then dried at room temperature and then pulverized and passed through a sieve. The dissolution rate of poorly soluble drug is increased when the reduced particle size of the drug deposited on the carrier which enhanced wettability of the particles brought about by the carrier [(94)].

1.2.8.5 Kneading technique:

In this method, carrier is saturated with water or organic solvent and transformed to paste. Drug is then added and kneaded for particular

time. The kneaded mixture is then dried and passed through sieve if necessary [54].

1.2.8.6 Gel entrapment technique:

Carrier which have tendency to swell is dissolved in suitable organic solvent to form a clear and transparent gel. The drug is then dissolved in gel by sonication for few minutes. Organic solvent is evaporated under vacuum. Solid dispersions are reduced in size by glass mortar and sieved [91].

1.2.9 Physical mixture method:

The physical mixtures were prepared by weighing the calculated amount of drug and carriers and then mixing them in a glass mortar by triturating. The resultant physical mixtures were passed through sieve and stored in desiccators [71].

1.2.10 Solid dispersion marketed products:

A list of several marketed products prepared using different solid dispersion techniques is given in table (1-12) [72, 76].

Table (1-10): Commercially marketed solid dispersions [72, 76]

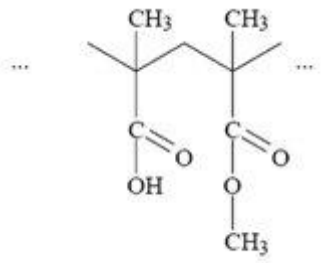
S.No.	Commercial products	Dispersion Polymer or Carrier used	Manufacturer Company
1	Gris-PEG® (Griseofulvin)	Polyvinylpyrrolidone (PVP)	VIP Pharma
2	Intelence® (Etravirine)	Hypromellose, and microcrystalline cellulose	Tibotec, Yardley, PA
3	Sproramax capsules (Itraconazole)	Hydroxypropylmethylcellulose (HPMC)	Janseen pharmaceutica
4	lopinavir and ritonavir	Polyvinylpyrrolidone–vinyl acetate copolymer	Abbott Laboratories, Abbott Park, IL
5	Afeditab (Nifedipine)	Poloxamer	Élan Corp

1.3 Polymers used for solid dispersion preparation in this study:

1.3.1 Eudragit L100

Eudragit L100 is first marketed in 1977. Anionic copolymers based on polyacrylates and polymethacrylates are glassy substances that are produced by the polymerization of acrylic and methacrylic acid, and derivatives of these polymers such as esters, amides and nitriles [95].

Structural formula:



Chemical name: Poly (methacrylic acid methyl methacrylate) 1: 1
Molecular weight: The relative molecular mass of about 135000 g/mol. The ratio of carboxylic acid to ester groups is about 1: 1.

Functional category: Film former; tablet binder; tablet diluent. It used for improvement of bioavailability and solubility of Telmisartan by solid dispersion technique done by Niranjan Chivate in 2013,the result of SEM indicates that the polymer has formed a uniform coating over the individual drug particles thus resulting in the formation of spherical particles with improved crystal properties so enhance the solubility[96].

Description: Eudragit L-100 is a white, free flowing powder with at least 95% of dry polymers. It is soluble at pH > 6. It is readily soluble in neutral to weakly alkaline conditions (pH 6-7) and form salts with alkalis, thus

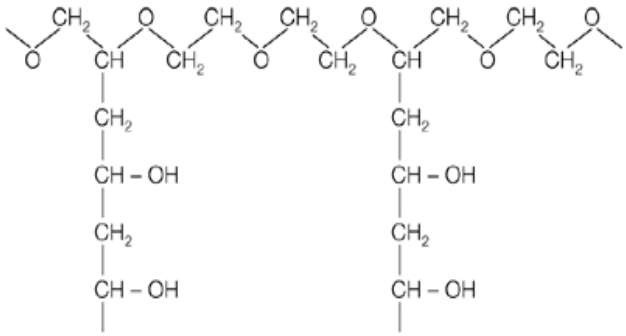
offering film coats which are resistant to gastric media, but soluble in intestinal fluid.

Solubility: It is freely soluble in acetone and sodium hydroxide. It is insoluble in dichloromethane, ethyl acetate, petroleum ether and water [97].

1.3.2 Kollicoat IR:

Kollicoat IR is a polyvinyl alcohol–polyethylene glycol graft copolymer. It was introduced to pharmaceutical research as an excipient and a film coating polymer with the aim of producing an immediate release dosage form and quick releasing formulation.

Structural formula:



Chemical name: is a poly(vinyl alcohol)-poly(ethylene glycol) graft copolymer (PVA-PEG)

Molecular weight: has a molecular mass of ~ 45,000 Da

Functional category: It is used as a pharmaceutical excipient that was especially developed as a coating polymer for instant release tablets. The polyvinyl alcohol moiety has good film-forming properties and also acts as an internal plasticizer and in the preparation of solid dispersions [98] as solid dispersions of itraconazole and Kollicoat IR with different ratios of drug to carrier. The dissolution profile shows that the drug dissolves rapidly and remains solubilized; because of the formation of amorphous phases, the drug can dissolve quickly along with Kollicoat IR[99] .

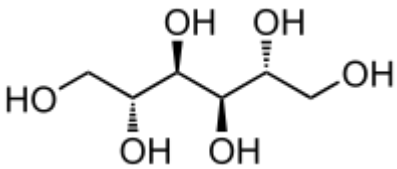
Description: Kollicoat IR is a white to faintly yellow free-flowing powder. The polymer is composed of ~ 75% PVA units and 25% PEG units, with PEG providing the backbone of the branched copolymer and PVA forming the branches The product also contains approx. 0.3% colloidal silica to improve its flow properties. As a result of its structure, It is non-ionic; its solubility does not change when the pH increases or decreases along the gastrointestinal tract. Though the viscosity of aqueous solutions of Kollicoat IR increases with the polymer concentration [100].

Solubility: The molecule is hydrophilic and thus readily soluble in water. Solutions of Kollicoat IR with concentrations of up to 40% can be prepared in water and aqueous systems, e.g. weak acids or alkalis. Solutions of up to 25% can be prepared in a 1:1 ethanol-water mixture. Due to colloidal silica, aqueous solutions of Kollicoat IR are slightly turbid [99].

1.3.3 D-Mannitol:

D-mannitol is a hexahydric alcohol related to mannose and is isomeric with sorbitol.

Structural formula:



Chemical name: D-Mannitol

Molecular weight: 182.17 g/mol

Functional category: Diluent for lyophilized preparations; sweetening agent; tablet and capsule diluent; tonicity agent.

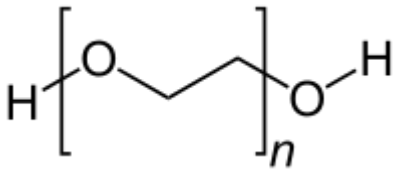
Description: occurs as a white, odorless, crystalline powder, or free-flowing granules. It has a sweet taste, approximately as sweet as glucose and half as sweet as sucrose, and imparts a cooling sensation in the mouth. Microscopically, it appears as orthorhombic needles when crystallized from alcohol. Mannitol, has a melting point of 165-168 °C and decomposes only above 250°C can be prepared as solid dispersion [101].

Solubility: Freely soluble in water1 in 5.5, sparingly soluble in ethanol (96 %) 1 in 83, practically insoluble in ether [101].

1.3.4 Polyethylene glycol (PEG4000):

Polyethylene glycols (PEG4000) are polymers of ethylene oxide,

Structural formula:



Chemical name: a-Hydro-o-hydroxy poly (oxy-1, 2-ethanediyl)

Molecular weight: Average molecular weight 3000–4800 g/mol

Functional category: Ointment base; plasticizer; solvent; suppository base; tablet and capsule lubricant. And in solid dispersion as for solubility enhancement of Mefenamic Acid, a poorly water soluble drug had done by Sanjeev Kumar [102].

Description: are white or off-white in color, they have a faint, sweet odor, free-flowing milled powders. Its melting point: 50–58°C for PEG 4000;

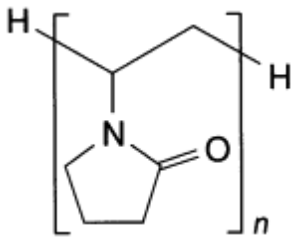
Solubility: are soluble in water and miscible in all proportions with other polyethylene glycols (after melting, if necessary) also are soluble in acetone, dichloromethane, ethanol (95%), and methanol; they are slightly

soluble in aliphatic hydrocarbons and ether, but insoluble in fats, fixed oils, and mineral oil [101].

1.3.5 Polyvinylpyrrolidone (PVP-K30) [101]:

PVP K30 has been used for the preparation of solid dispersion as a component of binary system for various drugs. The molecular size of PVP K 30 favors the formation of interstitial solid solutions

Structural formula:



Chemical name: 1-Ethenyl-2-pyrrolidinone homopolymer

Molecular weight: PVP K30 M.wt. 50 000 g/mol

Functional category: Disintegrants; dissolution aid; suspending agent; tablet binder.

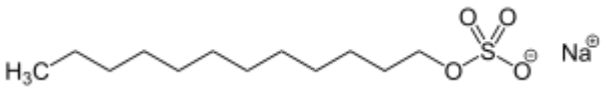
Description: occurs as a fine, white to creamy-white colored, odorless, hygroscopic powder.

Solubility: freely soluble in acids, chloroform, ethanol (95%), ketones, methanol, and water; practically insoluble in ether, hydrocarbons, and mineral oil.

1.3.6 Sodium lauryl sulphate (SLS):

Sodium lauryl sulfate is an anionic surfactant employed in a wide range of non-parenteral pharmaceutical formulations and cosmetics.

Structural formula:



Chemical name: Sulfuric acid monododecyl ester sodium salt

Molecular weight: 288.38 g/mol

Functional category: Anionic surfactant; detergent; emulsifying agent; skin penetrant; Solubilizer in concentrations greater than critical micelle concentration; tablet and capsule lubricant; wetting agent.

Description: Sodium lauryl sulfate consists of white or cream to pale yellow colored crystals, flakes, or powder having a smooth feel, a soapy, bitter taste, and a faint odor of fatty substances.

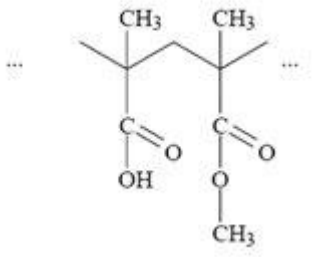
Solubility: freely soluble in water, giving an opalescent solution; practically insoluble in chloroform and ether [(101)].

1.4 Coating polymer for colon targeted delivery used in this study:

1.4.1 Eudragit S100:

Eudragit S100 is anionic copolymers based on methacrylic acid and methyl methacrylate.

Structural formula:



Chemical name: Poly (methacrylic acid-co-methyl methacrylate) 1:2

Molecular weight: approx. 125,000 g/mol

Physical properties: It is a solid substance in form of a white powder with a faint characteristic odor.

Targeted drug release area: Colon delivery as the dissolution at pH 7.

Uses: it can be used in the following cases:

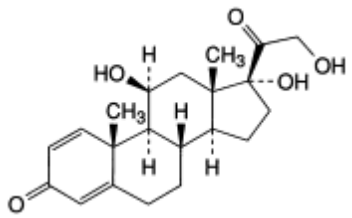
- Granulation of drug substances in powder form for controlled release
- Effective and stable enteric coatings with a fast dissolution in the upper Bowel
- Site specific drug delivery in colon [(103)].

1.5 Drug used for this study research:

1.5.1 Prednisolone [(104)]:

Chemical name: (11, 17-dihydroxy-17- (2-hydroxyacetyl)-10, 13-dimethyl-6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17-dodecahydrocyclopenta [a] phenanthrene3-one)

Structural formula:



1.5.2 Physicochemical properties:

White or almost white, crystalline, hygroscopic powder. Very slightly soluble in water, soluble in ethanol (96 percent) and in methanol, sparingly soluble in acetone, slightly soluble in methylene chloride. It has a molecular weight of 360.444 g/mol and melting point of 235°C [105].

1.5.3 Action and use:

Prednisolone (a potent synthetic corticosteroid that became available for clinical use in 1955) making it useful for the treatment of a wide range of inflammatory and auto-immune conditions such as Crohn's disease, Ulcerative colitis and rheumatoid arthritis and others [106, 107].

1.5.4 Pharmacokinetics of Prednisolone:

Prednisolone is completely absorbed from the GIT. When administered orally, around 80% of the prednisolone is absorbed. The bioavailability of prednisolone depends on the dissolution rate of the dosage form. Peak plasma concentrations of prednisolone are obtained 1 or 2 hours after an oral dose, and it has a usual plasma half-life of 2 to 4 hours. Its initial absorption, but not its overall bioavailability, is affected by food [108]. pKa not estimated as the chemical structure of prednisolone does not provide any acid or basic elements, and hence is a neutral substance and Log P 1.62[109].

Prednisolone is extensively bound to plasma proteins. It is highly protein bound (>90%) and excreted in the urine as either free or conjugated metabolites, with an appreciable proportion of unchanged prednisolone. It is insoluble in aqueous solutions and causes gastric irritation upon oral administration [109].

1.5.5 Dose and administration:

When given orally prednisolone, the usual dose, expressed in terms of prednisolone, is about 2.5 to 60 mg daily in divided doses, as a single daily dose after breakfast, or as a double dose on alternate days. Alternate-day early morning dosage regimens produce less suppression of the hypothalamic-pituitary axis but may not always provide adequate control. Enteric-coated tablets of prednisolone are also available. The lowest effective dose should be used for the shortest possible time; high doses may be needed for life threatening situations [110].

1.5.6 Preparations:

Prednisolone Tablets (uncoated) 5mg

Gastro-resistant Prednisolone Tablets (enteric coating) 5mg [104]

1.6 Previous work on aqueous solubility enhancement of Prednisolone:

1- Preparation of solid dispersions with various water-soluble carriers was studied to improve the dissolution of Prednisolone. The results indicated that *in vitro* dissolution rate of Prednisolone was remarkably improved in the solid dispersion of the drug compared with physical mixture and drug alone. This can be attributed to improved wettability, dispersibility, decrease in crystallinity, and increase in amorphous fraction of the drug [111].

2- Solid dispersion of prednisolone was prepared with PEG 6000 or different carbohydrates such as lactose and dextrin with various ratios of the drug to carrier. Solid dispersions were prepared by coevaporation method. The results indicated that lactose is suitable carriers to enhance the *in vitro* dissolution rate of prednisolone so, solid

dispersion of a poorly water-soluble drug, prednisolone may alleviate the problems of delayed and inconsistent rate of dissolution of the drug [112].

3- Encapsulation of pure prednisolone (PRD) and PRD–hydroxypropyl-β-cyclodextrin (HPβCD) complex in cellulose-based matrix microspheres. The system simultaneously exploits complexation technique to enhance the solubility of low-solubility drug (pure PRD) and subsequent modulation of drug release from microspheres (MIC) at a predetermined time [113].

1.7 Previous work on prednisolone for colon targeted drug delivery system:

1- A novel formulation for oral administration using Eudragit S 100 coated calcium alginate gel beads-entrapped liposome and prednisolone as drug has been investigated for colon-specific drug delivery *in vitro*. Drug release studies were done in conditions mimicking stomach to colon transit. Result shows that the drug was protected from being released completely in the physiological environment of the stomach and small intestine. The release rate of prednisolone from the coated calcium alginate gel beads-entrapped liposome was dependent on the concentration of calcium and sodium alginate, the amount of prednisolone in the liposome, as well as the coating [114].

2- Evaluate guar gum in combination with hydroxy propyl methylcellulose (HPMC) as compression coat for colonic delivery of prednisolone as well as improving the mechanical properties of the compressed coated tablets. The core tablets containing 5 mg prednisolone were compression coated with 125 mg of coating materials consisted of guar gum alone or mixtures of guar gum in combination with different ratios of HPMC. The results showed that tablets remained intact in stomach and small intestine, however partial and complete release of the

tracer occurred in the colon. In conclusion, guar gum in combination with HPMC would be successfully used as a carrier for drug delivery to the colon [115].

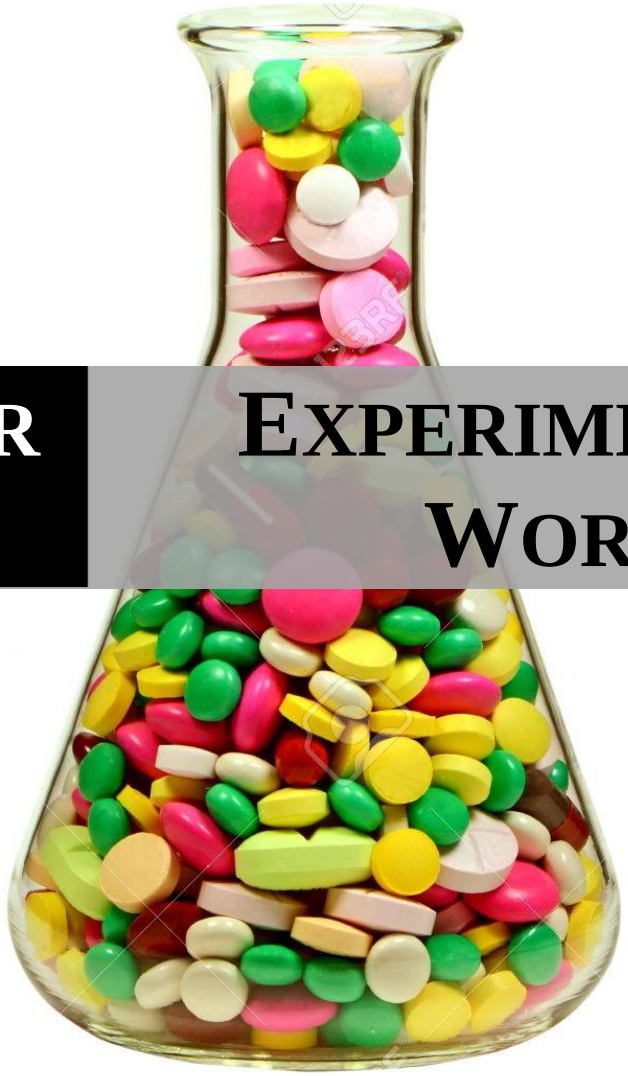
3- Formulation of prednisolone as an oral modified release tablet for colonic targeting. Many trials were performed to prepare a satisfactory formula using the wet granulation method with various additives and coatings. Result shows that lactose as a diluent provided the most reasonable release for prednisolone among other diluents. In addition, the formula containing 1% Eudragit RS PM was the best with regard to 100% release of drug in comparison with other concentrations and other retardant types. Avicel was used as a canalizing agent, and the results showed that the formula containing 30% Avicel PH 302 demonstrated faster release. Eudragit S 100 provided the best release of drug in phosphate buffer, pH 7.4, so in this study successfully formulated prednisolone-modified release tablets (coated matrix) using a wet granulation method as a potential colon delivery system [108].

The aim of the study

The aim of this study is to prepare and evaluate colon targeted tablets containing Prednisolone solid dispersions. Since solid dispersion technique can be used to enhance prednisolone solubility so this may lead to enhance its poor water solubility and then formulating these solid dispersions into tablets and target the release to colon by using pH-dependent system in order to have drug working at the site of disease (colon disease) this reducing the dose, frequency and some systemic side effect. Also studying the evaluation of the prepared solid dispersions and the tablets prepared using this solid dispersion to choose the best formula.

CHAPTER TWO

EXPERIMENTAL WORK



2. Experimental work

2.1 Materials

The materials used in this study and their manufacturers companies are listed in table (2-1).

Table (2-1): Materials used in the study

Material	Company
Acetone	Gainland chemical company, UK
Avicel pH302	Samara drug industry, Iraq
Croscarmellose sodium	Samara drug industry, Iraq
Crospovidone	Samara drug industry, Iraq
Deltacortril® (5mg tablet)	Pfizer, Turkey
Dibutyl phthalate	Fluka company, UK
D-Mannitol	Samara drug industry, Iraq
Absolute ethanol (96%)	Tedia company, USA
Eudragit L100	Sigma chemical co. (Aldrich), USA
Eudragit S100	Evonik company, Germany
Hydrochloric acid	Hopkin & Williams, UK
Isopropanol	BDH limited Poole, England
Kollicoat IR	Sigma chemical co. (Aldrich), USA
Magnesium stearate	Samara drug industry, Iraq
PEG 4000	Sinopharm chemical reagent co., china
Potassium dihydrogen orthophosphate	GCC Laboratory reagent, UK
Prednisolone	Samara drug industry, Iraq
PVP- K30	Samara drug industry, Iraq
SLS	Samara drug industry, Iraq
Sodium hydroxide	Thomas Barker(chemicals), India
Talc	Samara drug industry, Iraq

2.2 Instruments:

The instruments used in this study and their manufacturers are listed in Table (2-2)

Table (2-2): Instruments used in this study

Instrument	Manufacture
Digital balance	Kern, Germany
Dissolution apparatus	Cosmo lab. Equipment, India
Disintegration apparatus	Copley, Uk
DSC	Shimadzu, Japan
Friability test apparatus	Vanguard Pharmaceutical Machinery, USA
FTIR spectroscopy	Shimadzu 8400S, Japan
Hardness test apparatus	Vanguard Pharmaceutical Machinery, USA
Magnetic stirrer	Dragon Lab, USA
Melting point apparatus	Stuart SMP 30- UK
Oven	Memmert- Germany
pH meter	Inolab pH7110, china
Rotary evaporator	Buchi, Switzerland
SEM	SEM Tescan vega lll Czech
Sonicator	Elma- Germany
Tablet machine	Riva minipress, Germany
U.V. spectrophotometer	Shimadzu 1650 pc, Japan
Vernier	Copley, UK
X-ray diffractometer	Shimadzu, Japan

2.3 Methods

2.3.1 Characterization of drug used in the study:

2.3.1.1 Determination of prednisolone melting point:

The melting point of prednisolone was measured by the capillary method that complies with requirements of the british pharmacopeia (BP) and USP. The capillary tube was dipped in the powder and placed inside the melting point apparatus, the temperature was increased gradually, and the temperature at which the last particle passes into the liquid phase was recorded as melting point [116].

2.3.1.2 Preparation of reagents:

Preparation of simulated gastric fluid: 7 mL of hydrochloric acid was added to the distilled water in volumetric flask and the volume was made up to 1000mL using DW. The pH was finally adjusted to 1.2 using HCl or DW [117].

Preparation of buffering solutions (Phosphate buffer): To prepare buffer solution as colon media (phosphate buffer pH 7.4) 50mL of 0.2M potassium dihydrogen orthophosphate (prepared by weighing 27.22gms of potassium dihydrogen orthophosphate and dissolve in 1000mL of DW) was mix with 39mL of 0.2M NaOH (prepared by placing 8gms of sodium hydroxide and dissolve in 1000mL of DW) and the volume completed with DW up to 200mL. And to prepare buffer solution as intestinal media (phosphate buffer pH 6.8) 50mL of 0.2M potassium dihydrogen phosphate was mixed with 24mL of 0.2M NaOH and the volume completed with DW up to 200mL [118].

2.3.1.3 Determination of λ max of prednisolone:

Stock solutions of prednisolone (0.1mg/mL) in HCl (pH 1.2) and in phosphate buffer (pH 6.8 and 7.4) were prepared and suitably diluted then scanned by UV- visible spectrophotometer from 200-400 nm, and the λ max of the drug was determined.

2.3.1.4 Calibration curves of prednisolone:

Calibration curves of prednisolone in HCl solution (pH 1.2), phosphate buffer (pH 6.8 and 7.4) were obtained by reading the absorbance of serial dilutions from stock solution (0.1mg/mL) in each of the above three solutions, and the prepared samples were analyzed spectrophotometrically at the determined λ max. The measured absorbance of each sample was plotted versus concentration to obtain the standard calibration curve [119, 120].

2.3.1.5 Solubility determination of prednisolone:

For the determination of solubility of prednisolone, excess amount of the drug about (50 mg) was add to 25 mL phosphate buffers pH7.4 and the mixture in the flask was kept stirring using magnetic stirrer for 24 hours at 25ºC. The sample was then filtered through 0.45 µm membrane filter, suitably diluted, and analyzed by UV-spectrophotometer at 247nm for prednisolone. The study was performed in triplicate [121- 124].

2.3.1.6 Fourier transforms infrared spectroscopy (FTIR):

Sample of prednisolone powder (about 5 mg) were ground and mixed with dry potassium bromide and pressed in the form of a disc using hydraulic press. The disc was analyzed by FTIR spectroscopy (from 4000

to 400 cm^{-1}) [104] .

2.3.2 Preparation of prednisolone solid dispersion by solvent evaporation method:

Solid dispersions were prepared by solvent evaporation method. The solvent used to prepare the solid dispersions by this method was ethanol. Three different ratios of drug: polymers were formulated for each polymer (1:1, 1:2 and 1:3). The calculated amount of polymer and drug was dissolved separately in required amount of solvent ethanol and mixed under mechanical agitation. The solvent was evaporated using a rotary evaporator under reduced pressure. The dried solid dispersions were grinded in a mortar and pestle and passed through sieve(0.36 mm sieve) and stored in desiccators until use [125], and the optimum ratio for each carrier was compared with the drug:carrier physical mixture and pure prednisolone.The drug carrier weight ratios in solid dispersion and physical mixture are listed in table (2-3).

2.3.3 Preparation of prednisolone physical mixtures:

Accurately weighed quantities of prednisolone and carriers in the ratio of (1:3) were weighed and taken in a glass mortar, were mixed thoroughly for 10 min. The resultant mixture was passed through sieve and stored in a dessicator for the complete removal of moisture until used for further studies [126].

Table (2-3) Formulation code of Prednisolone solid dispersions and physical mixtures prepared with different carriers

Formulation Codes	Carrier	Drug: Carrier ratio (w/w)	Method of preparation
SD1	PEG4000	1:1	Solvent Evaporation
SD2		1:2	Solvent Evaporation
SD3		1:3	Solvent Evaporation
PM1		1:3	Physical Mixture
SD4	D- Mannitol	1:1	Solvent Evaporation
SD5		1:2	Solvent Evaporation
SD6		1:3	Solvent Evaporation
PM2		1:3	Physical Mixture
SD7	PEG/SLS(99:1%)	1:1	Solvent Evaporation
SD8		1:2	Solvent Evaporation
SD9		1:3	Solvent Evaporation
PM3		1:3	Physical Mixture
SD10	PVP-K30	1:1	Solvent Evaporation
SD11		1:2	Solvent Evaporation
SD12		1:3	Solvent Evaporation
PM4		1:3	Physical Mixture
SD13	Eudragit L100	1:1	Solvent Evaporation
SD14		1:2	Solvent Evaporation
SD15		1:3	Solvent Evaporation
PM5		1:3	Physical Mixture
SD16	Kollicoat IR	1:1	Solvent Evaporation
SD17		1:2	Solvent Evaporation
SD18		1:3	Solvent Evaporation
PM6		1:3	Physical Mixture

2.3.4 Evaluation of the prepared solid dispersion:

2.3.4.1 Determination of saturated solubility of prednisolone disperesed in solid dispersions:

The saturation solubility studies of disperesed drug was determined in phosphate buffer applying the procedure previously mentioned in paragraph (2.3.1.5) [127- 130].

2.3.4.2 *In vitro* dissolution study:

The *in vitro* dissolution study was carried out by using USP type II (paddle type) dissolution test apparatus (Cosmo Lab). Using 900 mL dissolution medium (pH 7.4) at 37°C and rotation speed of 50 rpm. Five mg of prednisolone and an equivalent amount from solid dispersions and physical mixtures to 5mg was placed in dissolution vessel for 90min and at appropriate time intervals (2, 5, 10, 15, 20, 30, 45, 60 and 90 min), 5 mL samples were withdrawn and replenished with the same volume of fresh medium to keep the sink condition constant, samples then filtered and analyzed spectrophotometrically at (247 nm for prednisolone). The procedure was performed in triplicate for each run test and the mean and standard deviation were calculated [131- 133].

2.3.4.3 Determination of drug content:

The drug content in each formulation was determined by weighing solid dispersion (equivalent to 2mg prednisolone) and transferring it to volumetric flask of 100mL and then phosphate buffer

(pH 7.4) was added gradually to the samples with continuous shaking to dissolve the sample. Finally the volume was made up to the 100mL. The samples were shaking for some time to dissolve the drugs completely and were filtered. The absorbance of the samples were determined at λmax 247 nm, using UV-visible spectrophotometer. Three reading were taken and then mean and standard deviation were calculated [134].

2.3.5 Factors affecting solubility and dissolution of solid dispersions:

2.3.5.1 Effect of drug:carrier ratio:

Formulas(SD1-SD3),(SD4-SD6),(SD7-SD9), (SD10-SD12), (SD13-SD15) and(SD16-SD18) were used for evaluating the effect of drug:carrier ratio on the drug solubility depending on phase solubility comparison. The effect of drug:carrier ratio on drug dissolution and release was also investigated by dissolution test.

2.3.5.2 Effect of carrier type:

Formulas SD3,SD6,SD9,SD12,SD15 and SD18) were utilized to investigate the effect of carrier type (PEG4000, Mannitol, PEG/SLS, PVP-K30, Eudragit L100, Kollicoat IR) respectively on Prednisolone solubility by comparing the changes in the phase solubility,and to investigate the effect of carrier type on drug dissolution and release.

2.3.5.3 Effect of preparation method:

Six sets of formulas of solid dispersion and physical mixture were compared to study the effect of the method of preparation on drug dissolution and release. The results were compared with the dissolution profile obtained from pure drug powder. The 1st set (SD3-PM1), 2nd set

(SD6-PM2), 3rd set (SD9-PM3), 4th set (SD12-PM4), 5th set (SD15-PM5) and 6th (SD18-PM6).

2.3.5.4 Effect of surfactant addition:

Formulas SD3 and SD9 were studied for the effect of adding a surfactant (SLS) on phase solubility and dissolution profile of the drug (prednisolone).

2.3.6 Selection of the best formula:

The phase solubility and *in vitro* dissolution test were used for selecting the best solid dispersion formula which will be subjected to further analysis.

2.3.7 Characterization of the selected solid dispersion formula:

2.3.7.1 Fourier transforms infrared spectroscopy (FTIR):

Samples of Kollicoat IR and SD18 (equivalent to about 5 mg of Prednisolone) were ground, mixed with dry potassium bromide and pressed in the form of discs using hydraulic press. The discs were analyzed by FTIR spectroscopy from (4000 - 400 cm^{-1}) [135, 136].

2.3.7.2 Differential scanning calorimetry (DSC):

The pure drug, polymer and solid dispersions were examined by DSC 60 (Shimadzu, Japan) where 5-6 mg samples were placed in aluminum pan at a heating rate of 10°C/min (in range of 0-350°C) with purging of dry nitrogen at a constant rate. an empty aluminium pan was used as reference. Indium/Zinc standards were used to calibrate the DSC temperature and enthalpy scale of the instrument. DSC was used to

determine thermal behaviour including m.p and solid state characterization of Prednisolone, Kollicoat IR and SD18 formulations [137, 138] done in Ministry of Science and Technology/ Iraq.

2.3.7.3 Powder x-ray diffraction (PXRD):

The extent of crystallinity was determined for pure drug and optimum formula of solid dispersion and physical mixture using PXRD system(Shimadzu, Japan) equipped with Cu radiation (λ=1.54060 A◦) at a voltage of (40 Kv) and a current of (30 mA).The instrument was operated in the continuous scan mode and sample were analyzed in the range (5-80◦)with a step size of (0.05 ◦) at scanning speed of (5◦/min) and(2θ) axis [111] done in Ministry of Science and Technology/ Iraq.

2.3.7.4 Scanning electron microscopy (SEM):

The SEM analysis was carried out using a scanning electron microscope (SEM Tescan vega lll czech). Prior to examination, samples were mounted on an aluminum stub using a double sided adhesive tape and then making it electrically conductive by coating with a thin layer of gold (approximately 20 nm) in vacuum. SEM provides a high resolution images that show details of a sample surface since a high energy beam of electrons typically from 0.5 kV to 40 kV is used to scan the surface of sample to give image in a raster scan pattern [139] done in Ministry of Science and Technology/ Iraq.

2.3.8 Manufacturing of colon targeted tablet of prednisolone by direct compression method:

2.3.8.1 Manufacturing of pure and solid dispersion uncoated tablets:

Pure and solid dispersions prednisolone were used in preparing tablets to evaluate the impact of solid dispersion on the release of the drug. Tablets ingredients powders mentioned in table (2-4) were accurately weighed then passed through 0.36 mm sieve to get uniform particle size. The drug and all the ingredients except lubricants were mixed and blended for 5 min. Finally magnesium stearate was added and again mixed for 2 minutes so that particle surface was coated by lubricant evenly. The blend was compressed using 6mm punch and die on single punch tablet machine. The formulated tablets were stored in a tightly closed container until evaluated. Based on dissolution study the best formulation was selected among all ten formulations for further study [140].

Table (2-4): Formulation of prednisolone and solid dispersions tablets

Ingredient (mg)	F1	F2 SD3	F3 SD3	F4 SD3	F5 SD6	F6 SD9	F7 SD9	F8 SD12	F9 SD15	F10 SD18
Prednisolone	5	-	-	-	-	-	-	-	-	-
Solid Dispersion	-	20	20	20	20	20	20	20	20	20
Cros-carmellose sodium	2	2	-	-	2	2	5	2	2	2
Cros-povidone	-	-	2	-	-	-	-	-	-	-
Magnesium stearate	1	1	1	1	1	1	1	1	1	1
Avicel PH302	92	77	77	79	77	77	74	77	77	77
Total weight	100	100	100	100	100	100	100	100	100	100

2.3.8.2 Pre-compression parameters evaluation:

Various micromeritic parameters like angle of repose, bulk density, tap density, Carr's (Compressibility) Index (CI), and Hausner's ratio were measured.

a- Angle of repose:

The angle of repose of powders was determined by the fixed funnel method. As the height of the funnel was adjusted as lower tip was at a height of exactly 1 cm above the surface [141] . The blends were poured till the time when upper tip of the pile surface touched the lower tip of the funnel. The powders were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation[142] :

$$\tan\theta = h/r, \quad \theta = \tan^{-1}[h/r]$$

where θ = angle of repose, h = height, and r = radius.

Table (2-5) shows the type of flow according to angle of repose values [143].

Table (2-5): The flow character according to angle of repose values [143].

Type of flow	Angle of repose (degrees)
Excellent	25-30
Good	31-35
Fair	36-40
Passable	41-45
Poor	46-55
Very poor	>56

b- Bulk density (D_b):

Bulk density calculated by using following equation [144].

D_b = (Mass powder)/Bulk volume of the powder

c- Tapped density (D_t) :

The tapped volume was measured by tapping the powder to constant volume after subjecting to 100 tappings in a graduated measuring cylinder and calculated by using following equation [145].

D_t = (Mass of powder)/(Tapped volume of the powder)

d- Carr's index:

It is calculated by using following formula, The value below 16% indicates a powder with usually good flow characteristics, whereas above 23% indicate poor flowability [146].

Carr's index= (Tapped density-Bulk density)/(Tapped density) ×100

e- Hausner's ratio:

It reveals the flow property of the powder material. It is the ratio of tapped density to bulk density of the powder and measured by employing the following formula [147].

Hausner ratio = D_t / D_b

Where D_t = Tapped density, D_b = Bulk density

2.3.8.3 Post-compression parameters evaluation:

a- Thickness test:

Thickness was calculated using vernier caliper [148, 149].Three tablets from each formula were used, and average values were calculated.

b- Hardness test:

The hardness of the tablets was determined using electrical Hardness tester. It is expressed in Kg/cm^2. The hardness test was performed in which five tablets from each formula were tested randomly and the average reading ± sd was recorded [150].

c- Weight variation test:

The weight variation test was analyzed by selecting twenty tablets randomly and average weights were determined. Then individual tablet weighed and compared with the average. The requirement met the USP; if not more than two tablets differ from the average weight ± 7.5 % and no tablet differs in weight by double that percentage, the tablets will be accepted [151].

$$\textbf{Calculate the average weight of tablets} = \frac{\textbf{Total weight of tablets}}{\textbf{Number of tablets}}$$

d- Friability test

The friability test was done by placing 20 pre-weighed tablets in the friabilator which was then operated for 25 rpm for 4 minutes; the tablets were then dusted and reweighed. Tablets that lose a maximum of

not more than 1% of their weight are generally considered acceptable. Percentage friability was calculated from the following equation[152]:

$$\textbf{\% Friability} = \frac{(W_\circ) - (W)}{(W_\circ)} \times 100$$

$W_\circ$ = weight of tablets before the test, W = weight of tablets after the test

e- Content uniformity test:

Content uniformity was done by weighing and powdering 20 tablets. Accurately weighted quantity of the powder equivalent to (5 mg of Prednisolone) was transferred to 100 mL volumetric flasks containing 50 mL of phosphate buffer pH 7.4. The flasks were shaken to solubilize the drug. The volume was made up with the buffer to 100 mL, mixed well and allowed to stand for 24 h to ensure complete solubility of the drug. The solution was filtered and 1 mL of the filtrate liquid was suitably diluted and analyzed for prednisolone content spectrophotometerically at 247 nm [142, 153].

f- *In vitro* disintegration study:

The *in-vitro* disintegration study of the uncoated tablets was determined using disintegration test apparatus as per USP specifications. one tablet was placed in each of the six tubes of the basket. the disc was add to each tube and running the apparatus using 900 mL of phosphate buffer pH 7.4 as the immersion liquid. The assembly should be raised and lowered between 30 cycles per min in immersion liquid maintained at 37ºC [154] .The time in seconds for complete disintegration of the tablets with no palpable mass remaining in the apparatus was measured and recorded [155].

g- *In vitro* dissolution study:

The *in vitro* dissolution study was carried out as mentioned previously in section (2.3.4.3) except that one tablet of each prepared formula was placed in dissolution vessel instead of powdered samples for 90min [138].

2.3.9 Variables affecting the dissolution profile of prednisolone uncoated tablets:

2.3.9.1 Effect of croscarmellose sodium concentration:

Formulas F6SD9 and F7SD9 were designed to study the effect of croscarmellose sodium (as superdisintegrant) concentration on the drug release from uncoated tablet, where 2 and 5% of croscarmellose sodium were used respectively.

2.3.9.2 Effect of different superdisintegrants addition in uncoated tablet:

Formulas F2SD3, F3SD3 and F4SD3 were designed to study the effect of different superdisintegrants addition on drug release of uncoated tablet compared with tablet prepared without the addition of superdisintegrant, where 2% croscarmellose, 2%crospovidone and no superdisintegrant were used respectively.

2.3.10 Eudragit S100 coating (pH- dependent system) of tablets for colon targeted delivery:

For minimizing drug release in upper GIT(stomach and small intestine) Eudragit S100 was selected as the pH dependent coating polymer. A 6% w/v Eudragit S100 coating solution was prepared using

mixture of isopropyl alcohol and acetone with the addition of 1% plasticizer(Dibutyl phthalate) and talc, this done by preparing two solutions 1st for the polymer and 2nd for plasticizer with talc individually then mix them together to be used to coat tablet of optimized formula using dip coating method (5times dipping) [156] .

2.3.11 Evaluation of the prepared coated tablets:

2.3.11.1 Thickness, hardness , friability and drug content tests:

Tablet of optimum formula was coated around the selected uncoated tablet formula and the resultant coated tablets evaluated for thickness, hardness, friability and drug content in the same way for uncoated tablets.

2.3.11.2 Disintegration test for enteric coated tablets:

The disintegration test was carried out for the selected solid dispersion coated tablets according to british pharmacopeia method for enteric-coated tablets HCl pH (1.2) and 7.4 pH phosphate buffer was used as media. Six tablets were used in each case [157].

2.3.11.3 *In-vitro* drug release study of coated tablets of prednisolone:

The *in-vitro* dissolution studies were carried out in USP-II dissolution apparatus at a stirring speed of 50 rpm in 900 mL of dissolution media maintained at 37±0.5°C.

To mimic the GIT transit, the dissolution was carried in different bio-relevant media representing pH of particular anatomical region. For mimicking the gastric fluid in stomach, the dissolution was performed in

HCl (pH 1.2) for two hours, in phosphate buffer (pH 6.8) to simulate the small intestinal fluid for three hours and for another two hours in phosphate buffer (pH 7.4), simulating the colonic environment. Sample aliquots withdrawn at specific time intervals, were analyzed at 247 nm using UV-visible spectrophotometer [156, 158].

2.3.11.4 Drug-excipient interactions

The physicochemical compatibilities of the drug and the used excipients were tested by FTIR. Pure prednisolone, selected uncoated and coated tablets (which were previously grinded); were mixed thoroughly with potassium bromide. The potassium bromide discs were prepared by compressing the powder at a pressure in a hydraulic press and analyse in the ranges, (4000- 400 cm^{-1}) [159].

2.3.11.5 Stability study: Effect of temperature:

This study was done at accelerated thermal conditions (40, 50 and 60 ^{o}C). The tablets were stored in the ovens for three months. Samples were taken at 14 day intervals and the amount of Prednisolone was measured using UV absorbance at 247 nm, in phosphate buffer pH 7.4 [160].

2.3.11.6 Statistical analysis:

The results of the experiments are given as a mean samples ± standard deviation (sd) and were analyzed according to one-way analysis of variance (ANOVA) at which significant results ($p<0.05$) and non-significant ($p>0.05$).

CHAPTER THREE

RESULT & DISCUSSION

3. Result & Discussion

3.1 Characterization of prednisolone:

3.1.1 Determination of melting point:

The measured melting point of prednisolone was found to be 235^{o}C. This result is the same as reported in reference which indicates the purity of drug powder [161].

3.1.2 Determination of λ max:

Scanning the diluted solutions of prednisolone in phosphate buffer (pH 6.8) , (pH 7.4) and HCl (pH 1.2) was done by UV-spectrophotometer at 200-400 nm and λ max was found to be 247 nm in all of these solutions [162 - 164].

3.1.3 Calibration curves of prednisolone:

Figures (3-1), (3-2) and (3-3) show calibration curves of prednisolone in phosphate buffer (pH 7.4), (pH 6.8) and in HCl (pH1.2) respectively. Straight lines were obtained by plotting the absorbance versus the concentration with high regression coefficient; this indicates that the calibration curves obey Beer's law within the range of concentration used.

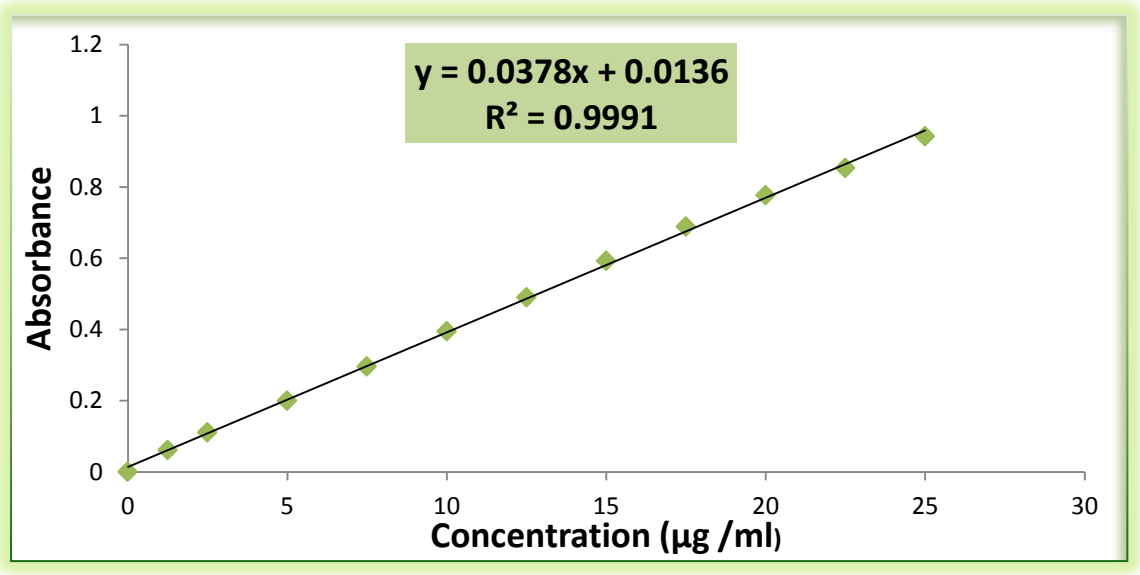


Figure (3-1): Calibration curve of prednisolone in phosphate buffer pH7.4.

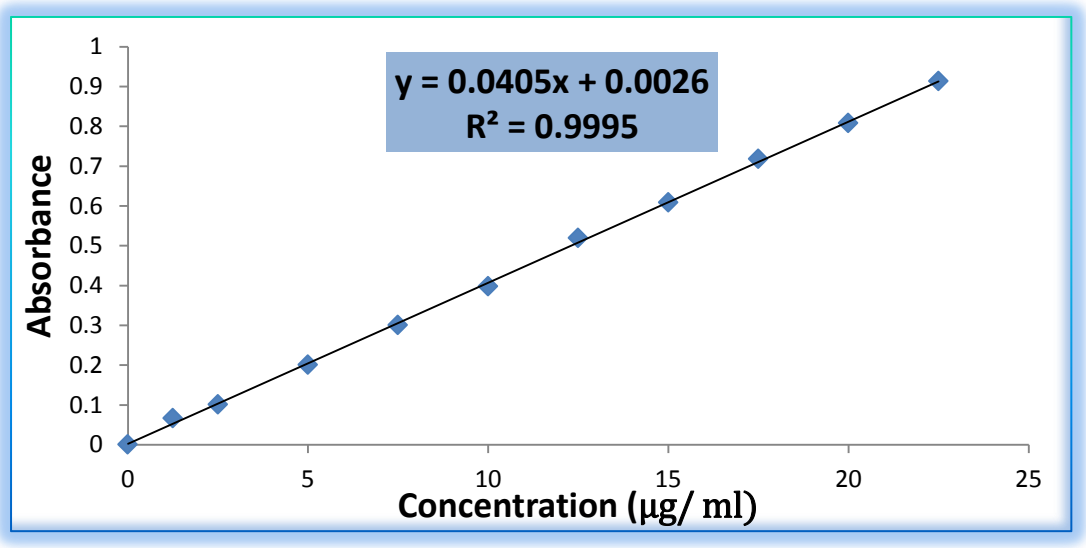


Figure (3-2): Calibration curve of prednisolone in phosphate buffer pH6.8.

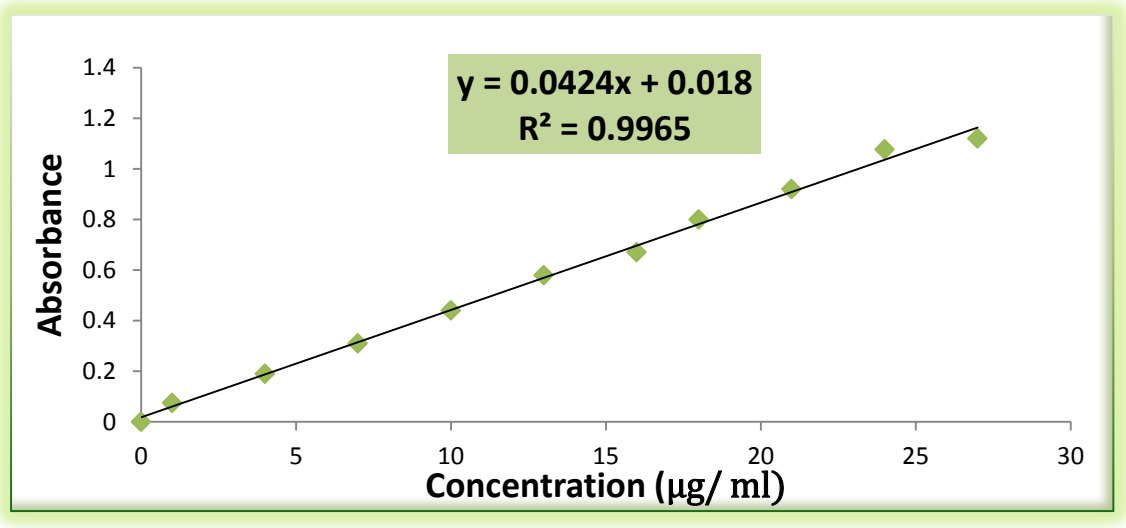


Figure (3-3): Calibration curve of prednisolone in HCl (pH 1.2)

3.1.4 Fourier transforms infrared spectroscopy (FTIR):

The FTIR spectrum for the pure prednisolone is shown in figure (3-5) which had all characteristic peaks of prednisolone when compared with reference FTIR spectra reported by japanese pharmacopoeia (Figure 3-4) and the most important peaks were listed in table (3-1).

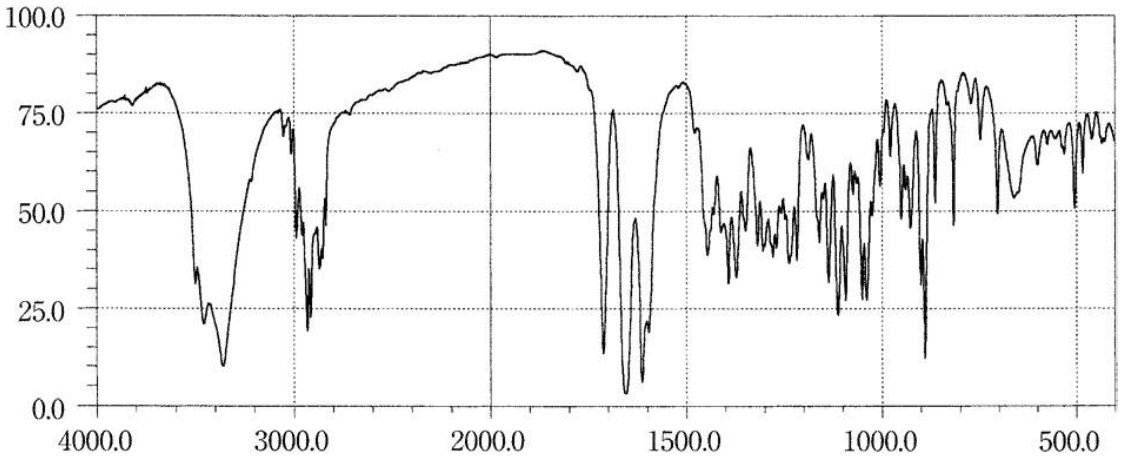


Figure (3-4): Prednisolone FTIR spectra reported by Japanese Pharmacopoeia [161].

Table (3-1): Characteristic peaks value of FTIR spectra of prednisolone

Type of Vibration	Observed freq.	Type of Vibration	Observed freq.
-OH	3454 cm^{-1}	C-H bend	1446 cm^{-1}
Sp3 C-H	2982 cm^{-1}	OH bend	1348 cm^{-1}
-C=O	1710 cm^{-1}	-C-O	1236 cm^{-1}
-C=O	1654 cm^{-1}	Aromatic C=C bend	893 cm^{-1}
Aromatic C=C	1610 cm^{-1}		

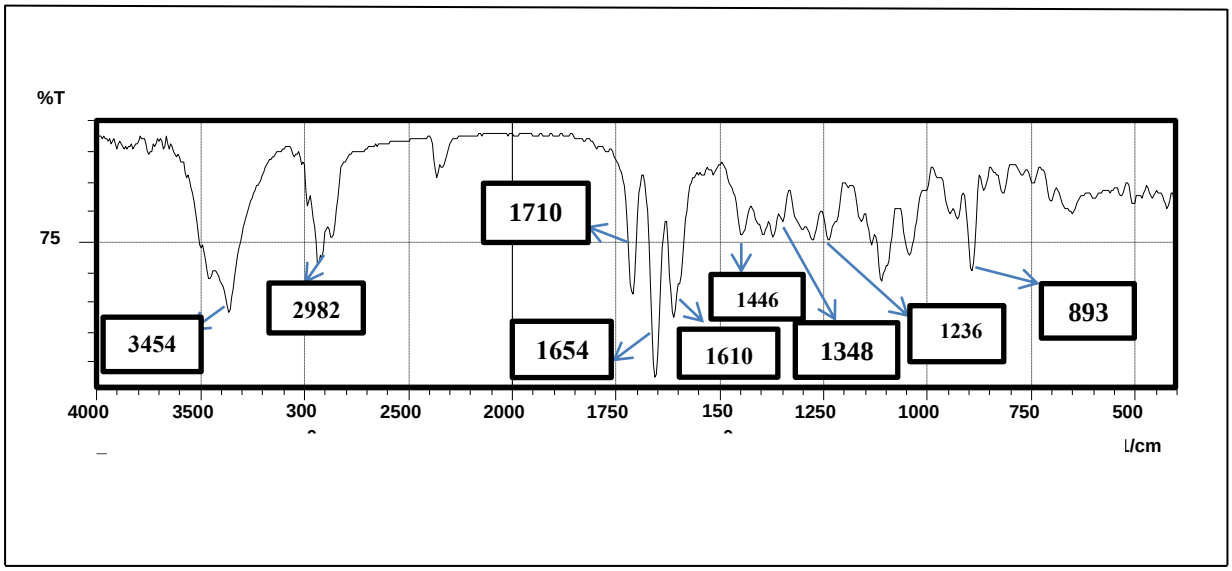


Figure (3-5): Prednisolone FTIR spectra

3.2 Evaluation of the prepared solid dispersion

3.2.1 Solubility studies of prednisolone and solid dispersion (Phase solubility):

The measured solubility of prednisolone in phosphate buffer pH 7.4 (215± 0.005 µg/mL) indicates that the drug is a very slightly soluble compound in this buffer. Solubility studies revealed a linear increase in drug solubility in the presence of an increasing carrier concentration with R^2 value between 0.9599 and 0.9992 as in figures (3-7) to (3-12). Similar

results have been reported for many drugs using the same carriers and several other hydrophilic carriers which have been attributed to the formation of weak soluble complexes. Hydrophilic carriers are known to interact with drug molecules mainly by electrostatic forces and occasionally by other types of forces like intermolecular hydrogen bonds (129,165,166).

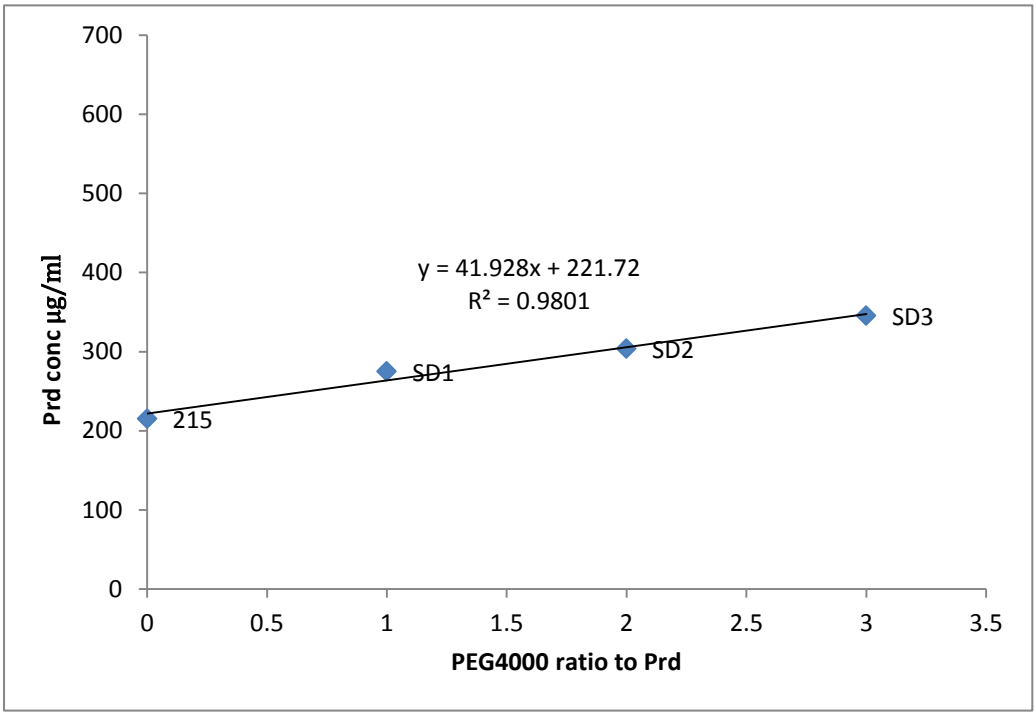


Figure (3-6): Phase solubility diagram of prednisolone (in phosphate buffer pH 7.4 at 25°C) in the presence of PEG4000.

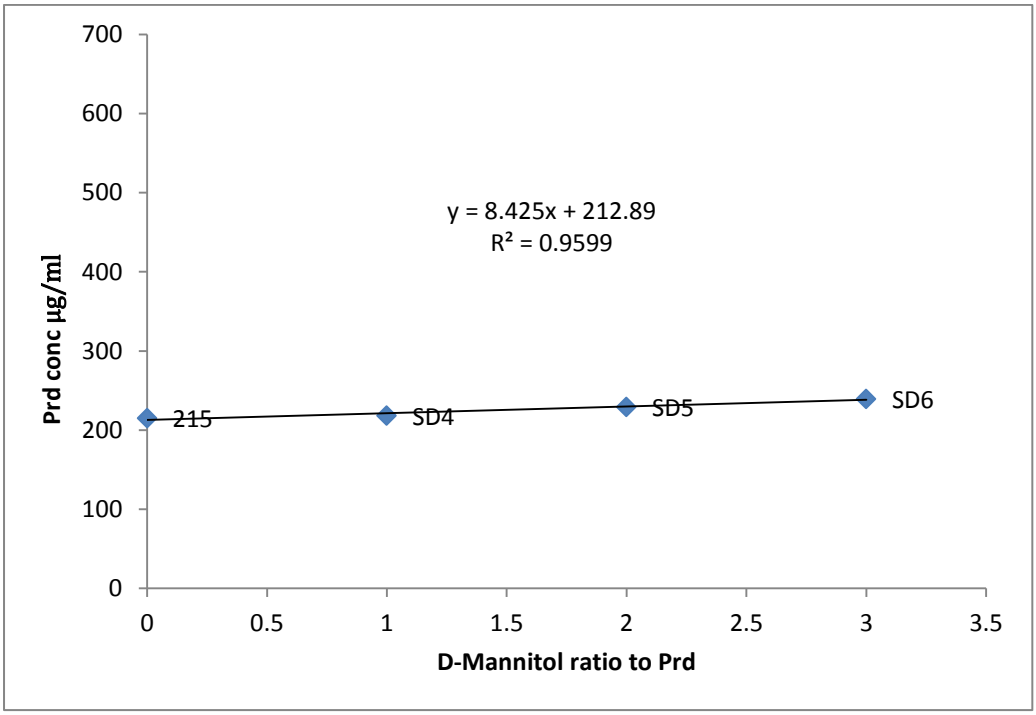


Figure (3-7): Phase solubility diagram of prednisolone (in phosphate buffer pH 7.4 at 25°C) in the presence of D-Mannitol.

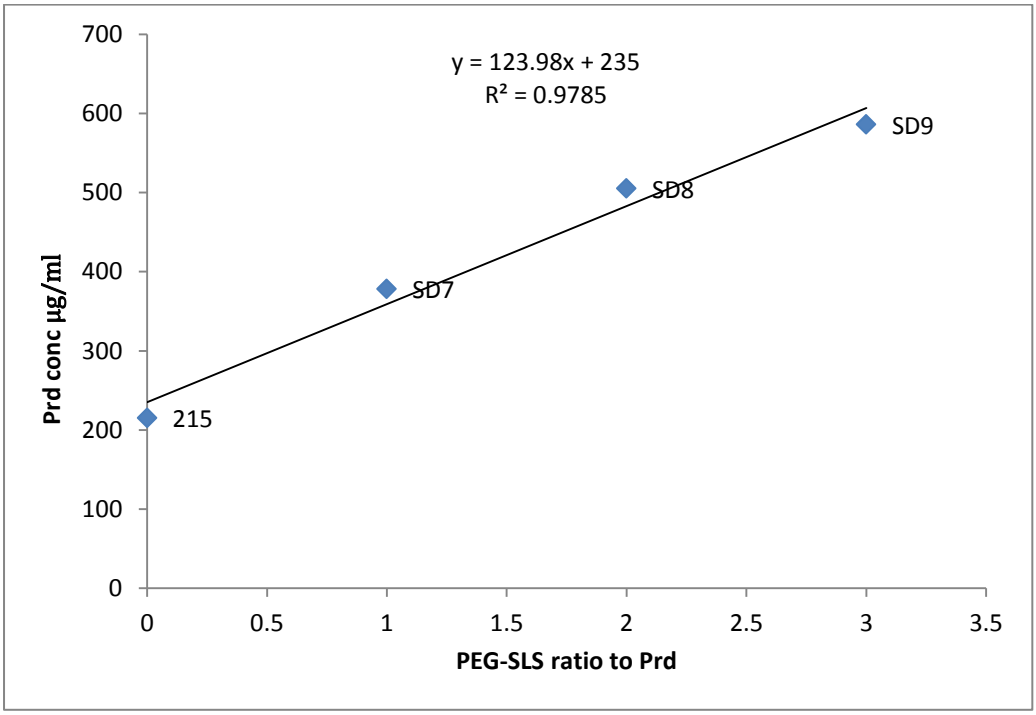


Figure (3-8): Phase solubility diagram of prednisolone (in phosphate buffer pH 7.4 at 25°C) in the presence of PEG-SLS.

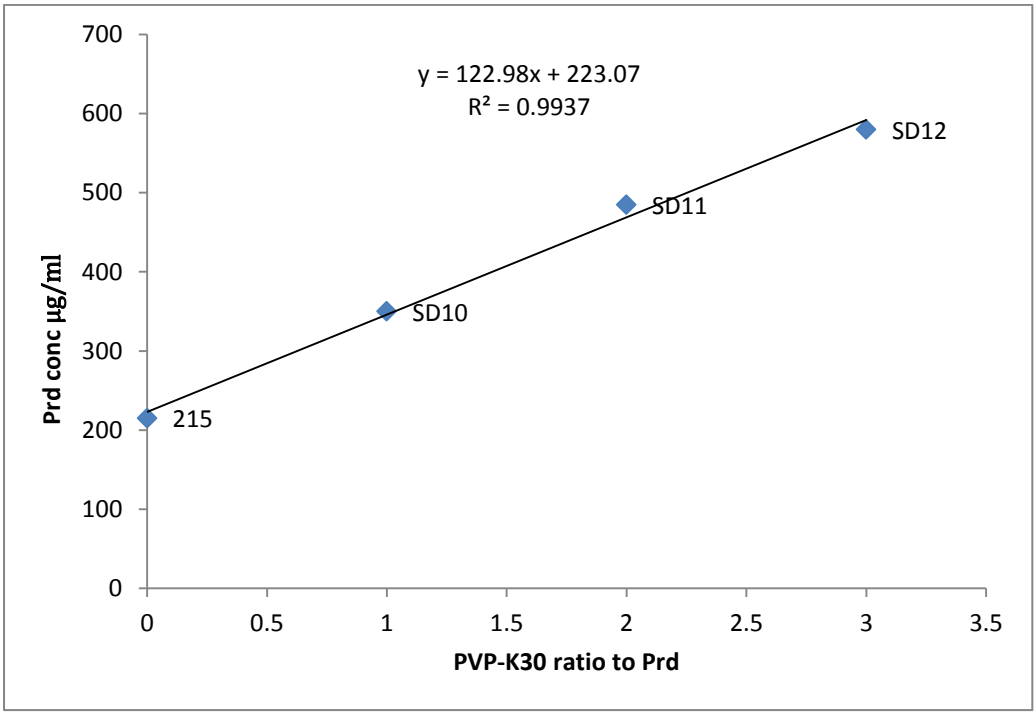


Figure (3-9): Phase solubility diagram of prednisolone (in phosphate buffer pH 7.4 at 25°C) in the presence of PVP-K30.

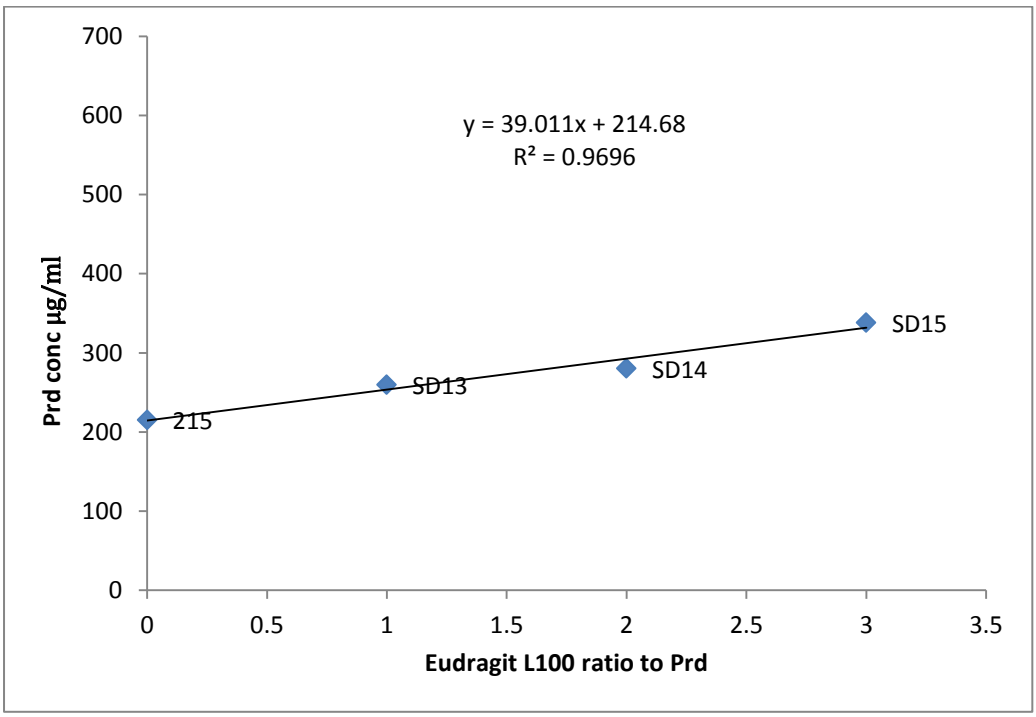


Figure (3-10): Phase solubility diagram of prednisolone (in phosphate buffer pH 7.4 at 25°C) in the presence of Eudragit L100.

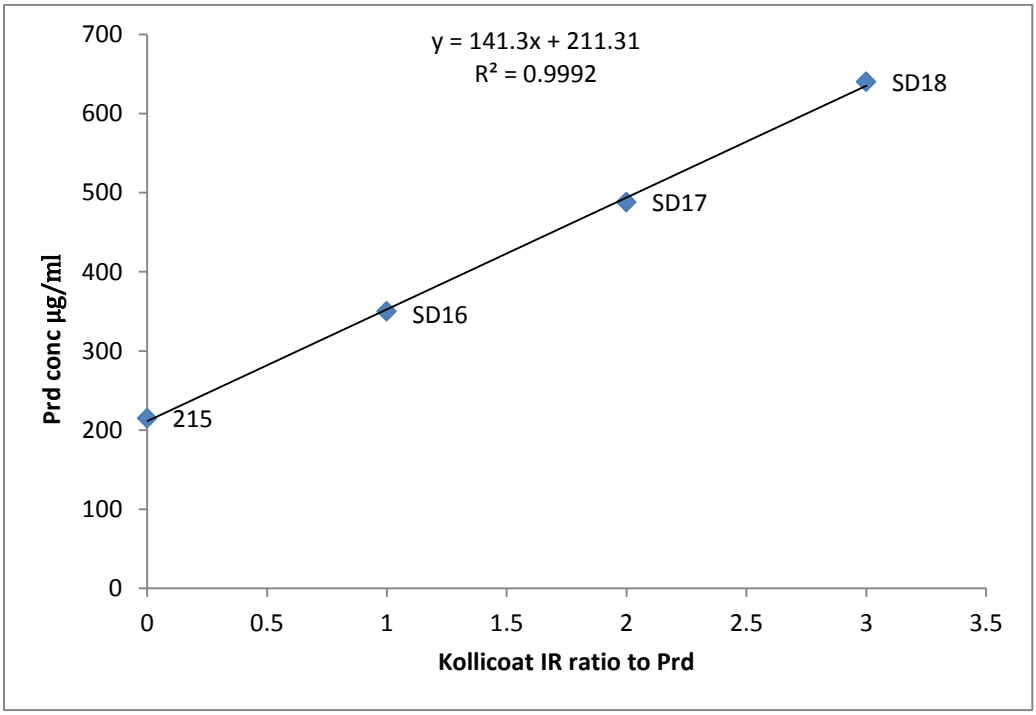


Figure (3-11): Phase solubility diagram of prednisolone (in phosphate buffer pH 7.4 at 25°C) in the presence of Kollicoat IR.

The result of solubility enhancement by carriers used was in the order of Kollicoat IR > PVP-K30 > PEG-SLS > PEG4000> Eudragit L100 >D-Mannitol. Figure (3-13) shows phase solubility of prednisolone in the solutions of the maximum ratio used (1:3) from each carrier. The markedly higher solubility of prednisolone in Kollicoat IR may be attributed to the higher solubilizing capacity of Kollicoat IR as it is non-ionic polymer; its solubility is pH-independent. Compared to other carriers used its surface activity and low viscosity when it is dissolved in solvent are advantageous to its use in solid dispersions, also the melting endotherms confirm that both the PEG and PVA parts of Kollicoat IR are at least semi crystalline in nature. After solid dispersion preparation, Kollicoat IR was more amorphous than the starting material [(98)], also because of the formation of unstructured /amorphous phases; the solubility is very high since the drug simply dissolved along with the hydrophilic polymers [(137)].

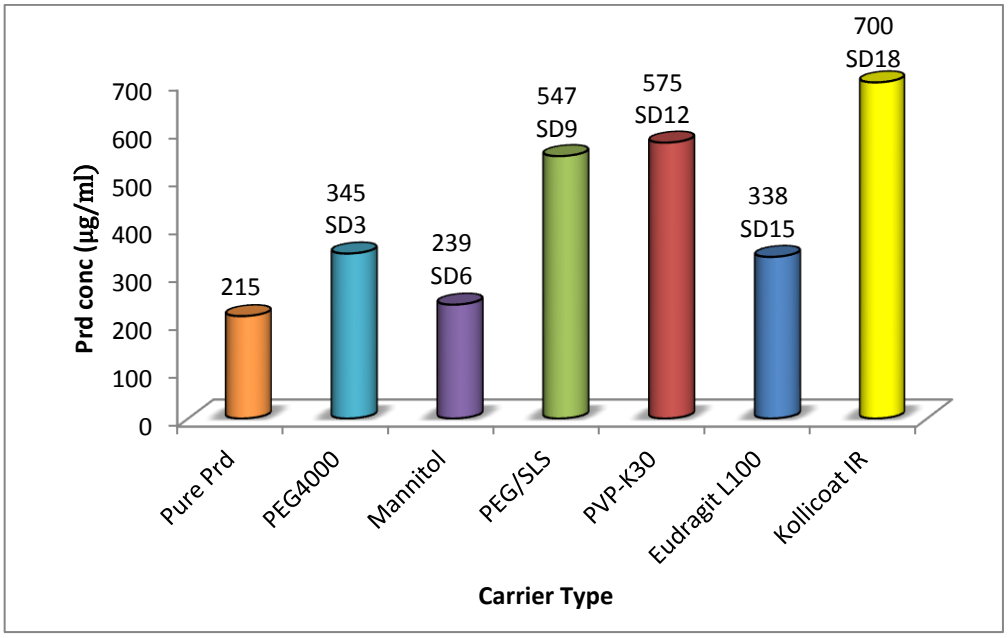


Figure (3-12): Phase solubility of prednisolone (in Phosphate buffer pH7.4 at 25°C) in the presence of different carriers at a drug: carrier ratio of 1: 3.

3.2.2 Determination of prednisolone content in solid dispersion formulas:

The content of prednisolone was determined in all the selected solid dispersion formulas prepared for each carriers and was found in the range (98 -101 %) of the theoretical calculated content which is within the limits of the official monographs of prednisolone preparations of the british pharmacopeia (100 ± 3% of the stated amount) which indicates a uniform distribution of prednisolone in the carriers as a result of the efficient method of preparation.

3.2.3 *In-vitro* dissolution study of prednisolone from pure powder and solid dispersion formulations:

The dissolution results of pure and solid dispersion of Prednisolone are shown in figure (3-14) and in terms of percent of drug dissolved at 5, 10, 15, 20 and 30 minutes shown in table(3-2).

It is evident that all prednisolone solid dispersions exhibit fast dissolution rate than pure drug. However the rate of dissolution was varying among different prednisolone solid dispersions (prepared using different types of carrier and ratios). Figure (3-14) shows that in the initial stage of dissolution formula SD18 and SD12 exhibited the highest drug release; about 100% and 96% of prednisolone was dissolved during the first 5 minutes respectively, compared to only32% prednisolone released from untreated prednisolone. Time for 100% of drug released from other solid dispersion formulas was varies between 15-30 min as shown in table (3-2). This significantly higher ($p< 0.05$) dissolution rate obtained from solid dispersion formulations was attributed to several factors as reduction in particle size [(167)], formation of higher energy metastable state with higher degree of amorphization of the drug, improved wetting properties, local solubilization of the carrier at the diffusion layer [(168)], increased porosity, and the formation of intermolecular hydrogen bonding between the drug and the carrier [(169)].

Table (3-2): Dissolution parameters of the prepared prednisolone solid dispersions.

No. of formula	PD5min	PD10min	PD15min	PD20min	PD30min
Pure drug	32	42	46	50	56
SD1	36	58	65	75	90
SD2	61	65	70	78	94
SD3	72	80	86	89	99
SD4	40	63	73	82	93
SD5	62	77	79	82	95
SD6	78	78.5	81	85	96
SD7	43	58	66	77	92
SD8	79	80	80	84	95
SD9	83	86	89	95	99
SD10	40	51	60	70	89
SD11	70	79.5	88	90	94
SD12	96	100	99.5	99.5	100
SD13	40	55	66	75	80
SD14	60	76	80	85	96
SD15	75	85	91	93	99
SD16	47.3	64	71	80	88
SD17	73	81.6	84	87.8	96
SD18	100	100	99.5	99.8	100

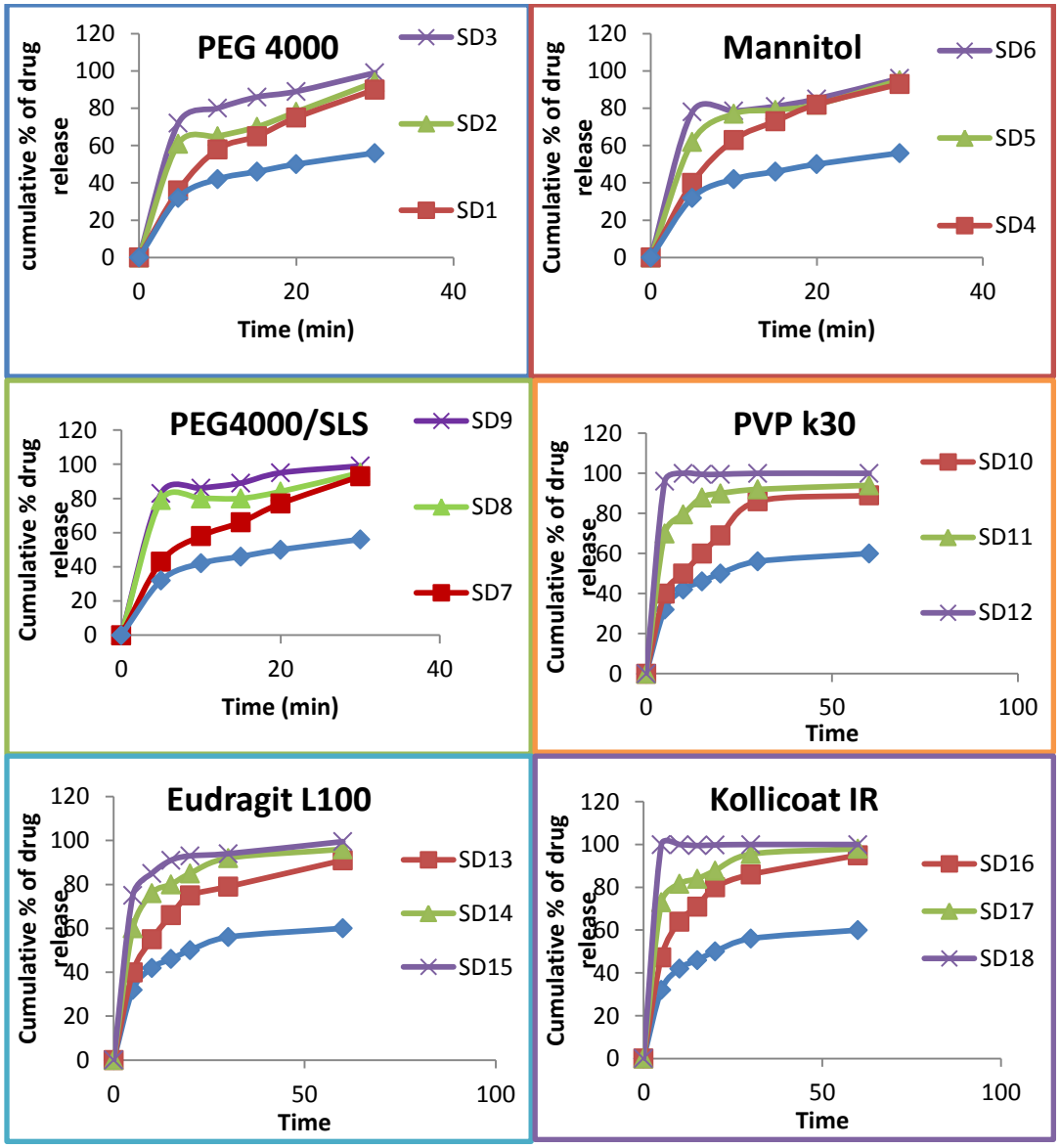


Figure (3-13): Effect of using different carrier ratio on drug release from different solid dispersion formulations in phosphate buffer pH7.4 at 37°C.

3.2.4 Effect of carrier type and formulation method by physical mixture and solid dispersion:

It was observed that the rate of release for PM1, PM2, PM3, and PM5 was lower than PM4 and PM6. As 85% and 90% prednisolone was found to be released in case PM4 and PM6 (1:3 ratio) after 30 minutes of dissolution respectively. The increase in dissolution rate of drug in the presences of carriers could be attributed to an increasingly effective

solubilization process. Because of the formation of unstructured/amorphous phases, the dissolution percentage is very high since the drug simply dissolved along with the hydrophilic polymers. Therefore, aqueous solubility improvement and little viscosity of Kollicoat IR enhance the dissolution process. On the other hand the formulations SD3, SD6, SD9, SD12, SD15 and SD18, produced by Solvent evaporation technique showed maximum release after time interval lower than that needed for physical mixture formulas. As example 5 minutes which were nearly 100 % for Kollicoat IR (SD18) and 96% for PVP-K 30 (SD12) which were much higher than SD3, SD6, SD9, SD15 and all other physical mixture formulations as shown in figure (3-15). Various studies have shown that Kollicoat IR inhibit crystallinity of drugs and resulting in amorphous nature of drug in the solid dispersions. Crystallization inhibition was attributed to two effects: the interactions between the drug molecule and the hydrophilic polymer due to hydrogen bonding and the entrapment of the drug molecules in the hydrophilic polymeric matrix [170]. In presence of Kollicoat IR, drug had better wettability; hence the dissolution of drug was greater in the form of solid dispersion [170].The results can be explained on the basis of carrier's chemical nature, where D-mannitol is crystalline carrier and it can form crystalline solid dispersion only (first generation solid dispersion) which is thermodynamically more stable and have limited capacity to increase the solubility of the poor water soluble drugs through particle size reduction and increasing wettability [171], where PEG4000 and Eudragit L100 and PVP K-30 are of second generation which form amorphous solid dispersion in general so they are better than D-mannitol and their enhancement for Prednisolone release in the order of PVP K30> Eudragit L100> PEG4000 but addition of surfactant such as SLS to PEG4000 resulted in formulation of solid dispersion of third generation which is the

dissolution profile could be increased by using mixture of amorphous polymers and a surfactant as carrier having surface activity and self-emulsifying characteristics to increase the solubility. The third generation solid dispersions increase the bioavailability of the poorly soluble drugs and reduce recrystallisation of drug [172].

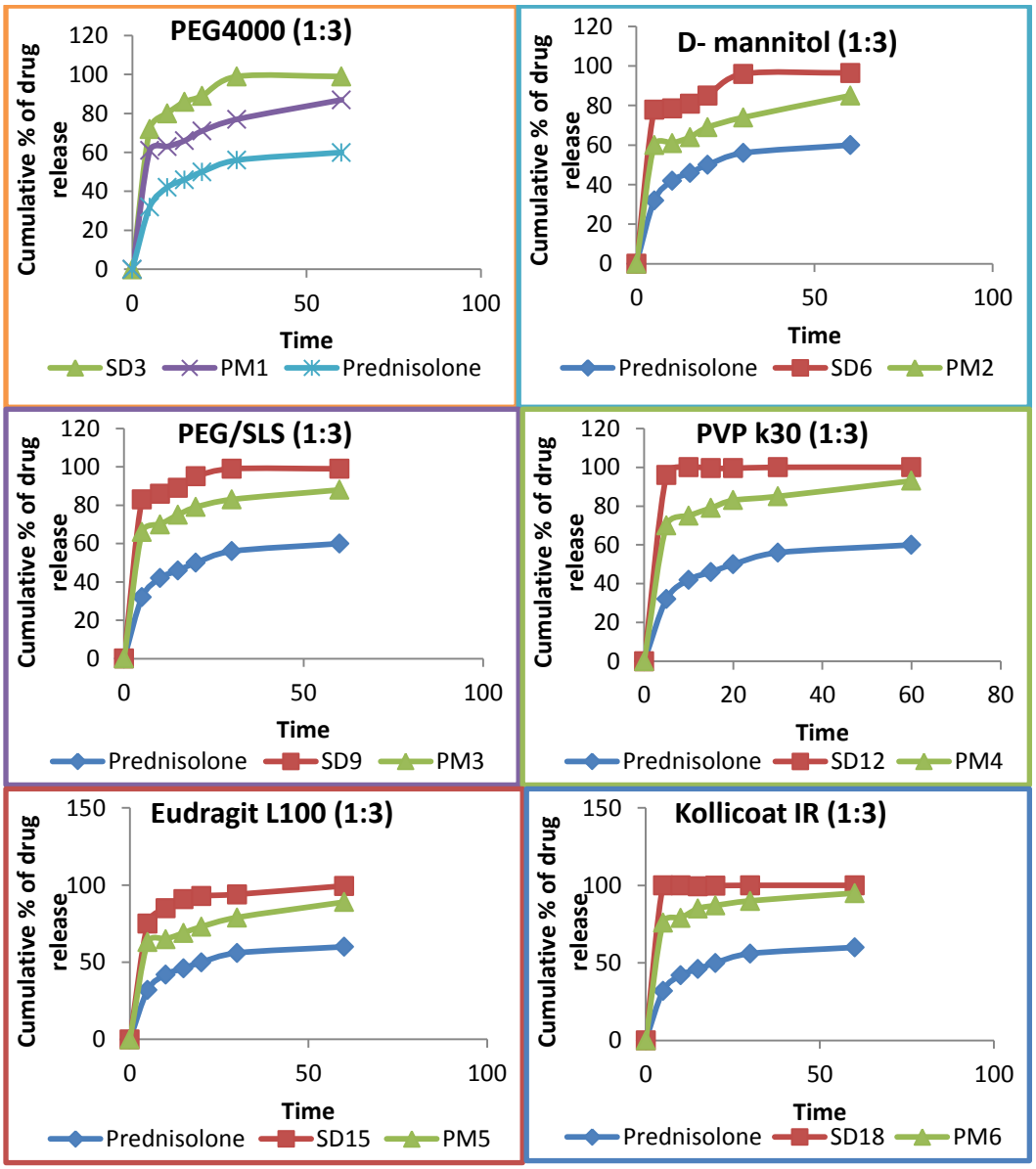


Figure (3-14): Effect of carrier type and formulation method on percent drug release in phosphate buffer pH7.4 at 37°C.

3.2.5 Effect of surfactant addition in solid dispersion formulation:

Effect of surfactant addition in the formulation of solid dispersion in the solubility was investigated using formula SD3 and SD9 the solubility enhancement increased by the addition of SLS from (345.16 ±0.002 to 585.9 ±0.001) µg/ml and also the percent drug release at 5 min from 72 to 83% all this due to the effect of addition of surfactant. Which is may be due to the fact that ternary dispersion prepared by solvent evaporation result in a more uniform dispersion of the drug in the hydrophilic carrier (PEG4000) so, addition of sodium lauryl sulphate improved the aqueous solubility and dissolution of prednisolone, similar result recorded for meloxicam [(173)].

3.2.6 Selection of the best formula of solid dispersion:

Since the aim of the work is to obtain a formula with the highest dissolution rate and extent, the selection of the best formulas will depend on the solubility and dissolution study from all the above result formula SD18 was chosen as best formula due to higher solubility and percent release of the drug are obtain therefore further characterization on this formula was done.

3.2.7 Characterization of the selected solid dispersion formula

3.2.7.1 Fourier transforms infrared spectroscopy (FTIR):

The FTIR spectrum of SD18 (Figure 3-16 c) was examined and matched with those of prednisolone, Kollicoat IR (Figures3-16a,b

respectively) for the changes in position or intensity of peaks as an indication of interactions such as hydrogen bonding.

In general, there is a reduction in the intensity and sharpness of the absorption bands of SD18 compared to Prednisolone alone as a result of formation of intermolecular hydrogen bonding between drug and carrier.

The FTIR spectrum of Kollicoat IR showed a characteristic band at 3421 cm^{-1}, which is assigned for OH stretching. No appearance of new bands suggesting no chemical interaction between the drug and the carrier. Reduction in the sharpness and smoothing of the peaks means a reduction of prednisolone crystallinity which can be further confirmed by DSC and PXRD study. The results are in agreement with that of a research on piroxicam [174, 175].

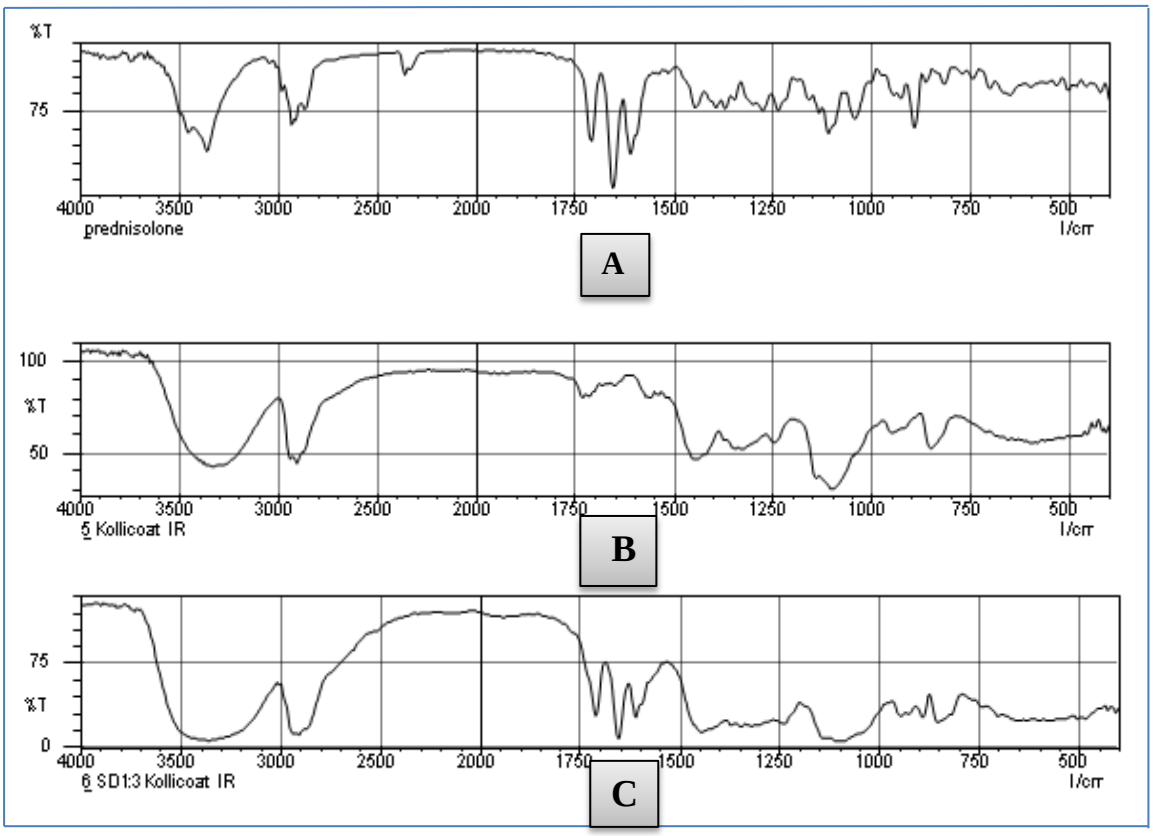


Figure (3-15): FTIR spectra of A- Prednisolone, B- Kollicoat IR and C- SD18.

3.2.7.2 Differential scanning calorimetry (DSC):

(DSC) is one of the thermal analysis techniques usually used for characterization the thermal behavior of drug substance in pure state and in pharmaceutical mixture. (DSC) is frequently the pharmaceutical thermal analysis technique of choice because of its ability to provide detailed information about both the physical and energetic properties of substances. The thermograms of prednisolone and Kollicoat IR (Figure 3-17) indicate their crystalline nature by exhibiting one endothermic peak corresponding to the melting point of the drug and the carrier respectively. The presence of single endothermic peak in the thermogram of SD18 at 203ºC (Figure 3-17) around the polymer melting point (m.p). The absence of m.p of drug in solid dispersion thermogram could be due to polymer fusion with the absence of a peak corresponding to prednisolone can be attributed to the possible dissolution of the drug in the molten carrier during heating cycle in DSC analysis [176] or might also due to the fact that drug might also transform from its crystalline form to amorphous form in the solid dispersion formulation which can be further supported by PXRD and FTIR results.

The results are in agreement with that of a research on Tenoxicam [175].

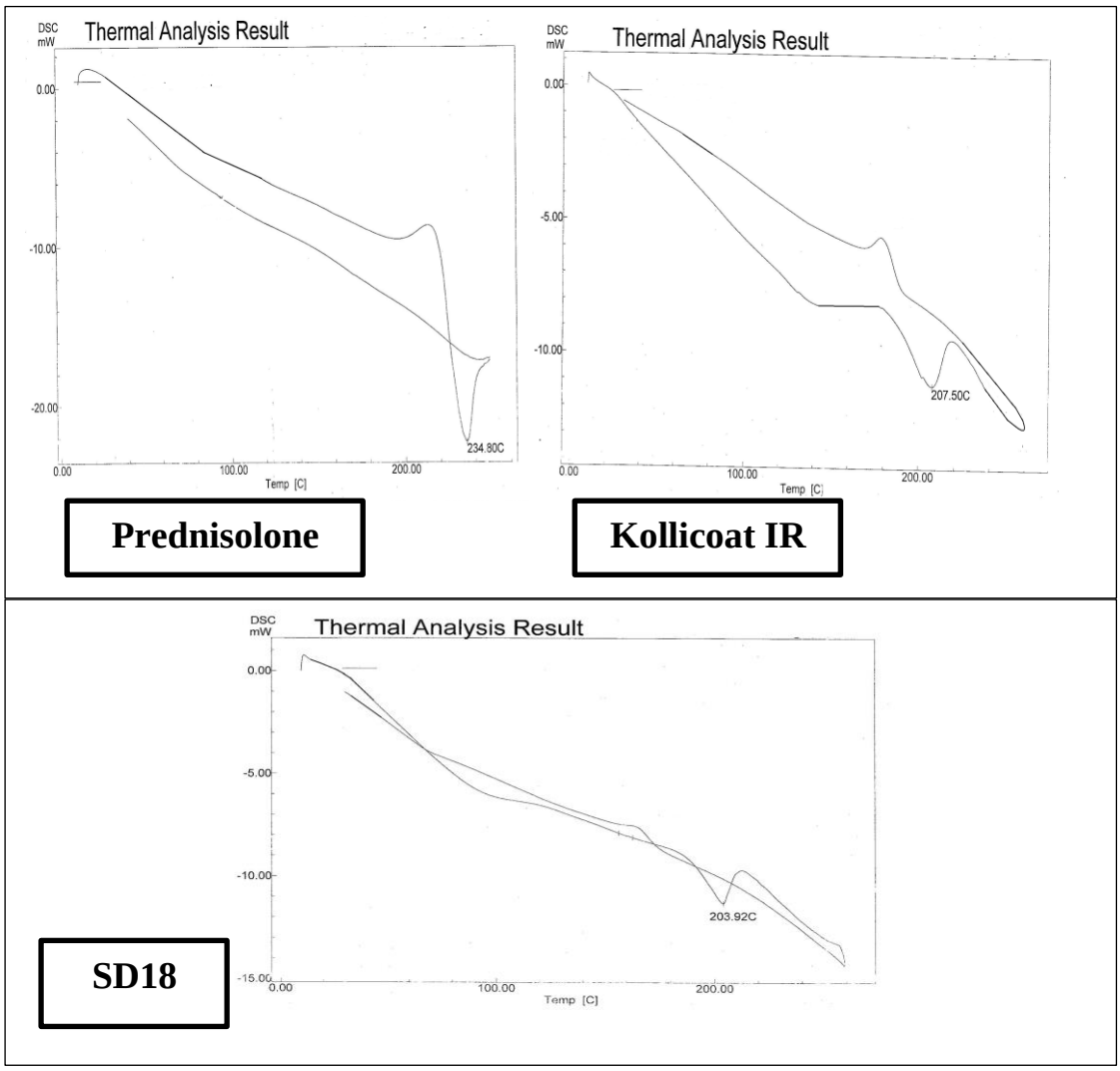


Figure (3-16): DSC thermogram of pure prednisolone, Kollicoat IR and SD18 (1:3 Kollicoat IR)

3.2.7.3 Powder x-ray diffraction (PXRD):

The solid state characterization of drug and solid dispersion were investigated using PXRD to find out crystalline nature of prednisolone and solid dispersion (1:3 Kollicoat IR). The diffraction spectrum of pure prednisolone showed that the drug was crystalline in nature as it was demonstrated by numerous peaks. As shown in figure (3-18) some changes in the peak positions of prednisolone were observed in SD18. Peak intensity was also decreased in solid dispersion. Highest peak intensity in case of pure prednisolone was 1442 counts; on the other hand

it was only 156 in case of SD and 412 in case of physical mixture. The relative reduction of diffraction intensity of prednisolone in SD 18 at these angles suggests that the size of the crystals was reduced. The results of this study imply that Prednisolone is present in partially amorphous or microcrystalline form in the solid dispersion. Also there is no appearance of new diffraction peaks which rules out any chemical interaction between the components or the existence of any other type of crystals [177].

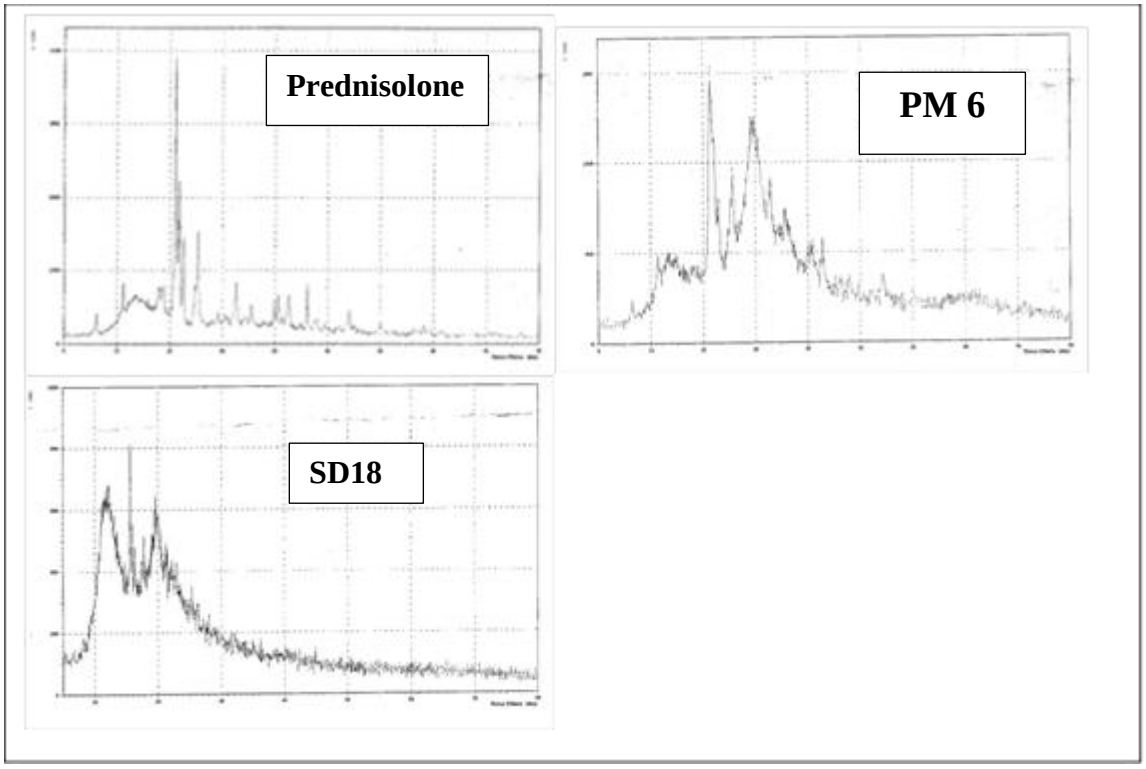


Figure (3-17): X-ray diffraction (PXRD) patterns of pure prednisolone, PM6 and SD18.

3.2.7.4 Scanning electron microscopy (SEM):

Microscopic investigations were undertaken on the pure drug, physical mixture and solid dispersion using SEM. Micrographs revealed that the particle size of prednisolone in the physical mixture is approximately of smaller size compared to pure drug. In contrast, the size of the particles of solid dispersion is smaller than that of the pure drug and

physical mixture. The smaller the particle size, greater the wetted surface area, and hence the better the solubility. (Figure 3-19) micrographs indicate that the pure drug is in crystalline form whereas physical mixture possesses amorphous particles and some crystals of the drug. In the case of the solid dispersion, the drug particles reduced in size, some have spherical shape might be one of the factors that are responsible for enhancing drug dissolution and solubility by providing large surface area in addition to surrounding drug particles by the hydrophilic Kollicoat IR particles. Particles are in an amorphous state, all these confirming formation of solid dispersion [175].

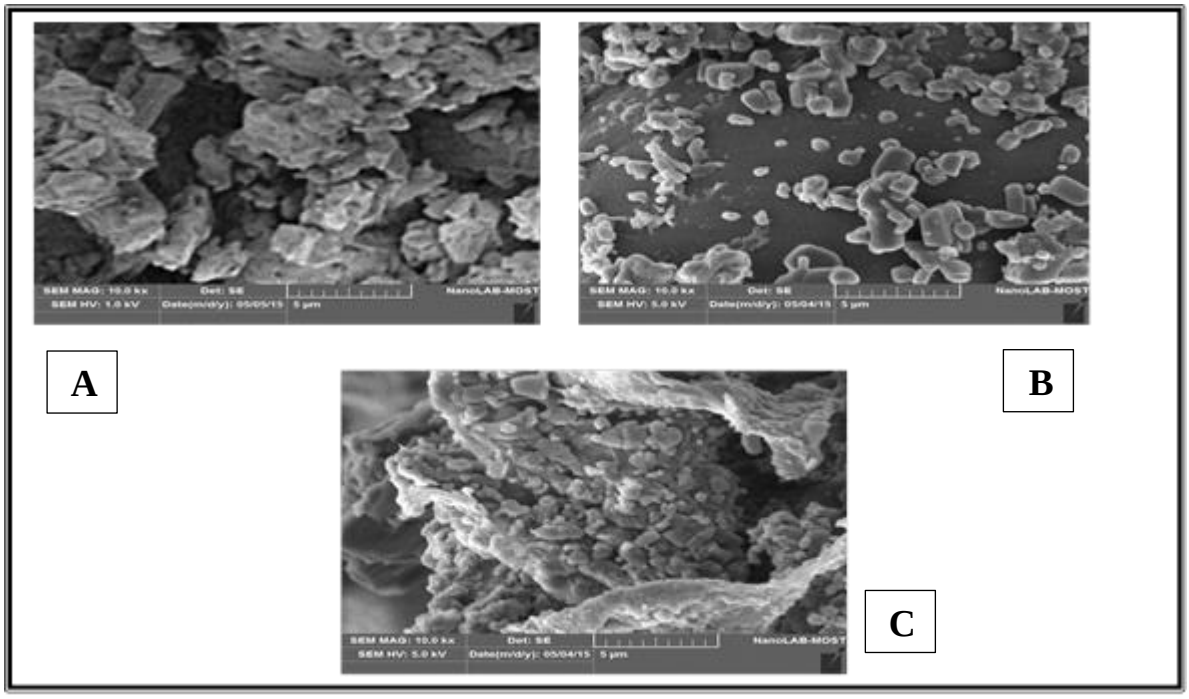


Figure (3-18): SEM of A-pure drug, B- physical mixture and C-SD18

All these result give explanation of higher solubility and faster release of drug from this solid dispersion formula compared to pure drug and physical mixture of the same ratio.

3.3 Prednisolone tablet manufacturing:

Direct compression is the simplest and most economical method for the manufacturing of tablets because it requires less processing steps than other techniques [178]. Pure drug and solid dispersion samples (SD3, SD6, SD9, SD12, SD15 and SD18) are formulated and compressed into tablets by direct compression method. Avicel PH302 was used as diluent, croscarmellose sodium was used as superdisintegrant and magnesium stearate as lubricant.

3.3.1 Evaluation of prednisolone prepared tablets

3.3.1.1 Pre-compression parameters of powder blend

Bulk density is defined as the mass of a powder divided by the bulk volume. The bulk density of a powder depends primarily on particle size distribution, particle shape, and the tendency of the particles to adhere to one another, Carr's index it helps in measuring the force required breaking the friction between the particles and the hopper during tableting. The values of angle of repose, bulk density, tapped density, Carr's index, and Hausner ratio for the prepared powder blend of each formula was illustrated in table (3-3). These results estimated according to USP [155]. The results show that the prepared mixtures have acceptable flow properties and compressibility.

Table (3-3): Pre-compression physical parameters for powder blend

Formula	Angle of repose (Degree)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's Index	Hausner ratio	Type of flow
F1 (Prd)	33.78±0.66	0.323±0.04	0.37±0.01	12.7	1.15	Good
F2 (SD3)	31.21±0.51	0.323±0.01	0.364±0.06	11.26	1.13	Good
F3 (SD3)	31.21±0.51	0.323±0.01	0.364±0.06	11.26	1.13	Good
F4 (SD3)	31.15±0.63	0.364±0.04	0.408±0.01	10.78	1.12	Good
F5 (SD6)	24.52±0.62	0.385±0.02	0.417±0.03	7.67	1.08	Excellent
F6 (SD9)	30.96±0.57	0.377±0.05	0.417±0.02	9.59	1.11	Excellent
F7 (SD9)	30.56±0.62	0.377±0.05	0.417±0.05	9.59	1.11	Excellent`
F8 (SD12)	26.44±0.69	0.388±0.01	0.415±0.05	6.51	1.07	Excellent
F9 (SD15)	26.56±0.62	0.364±0.04	0.408±0.01	10.78	1.12	Excellent
F10 (SD18)	33.17±0.64	0.345±0.03	0.408±0.04	15.44	1.18	Good

3.3.1.2 Post-compression parameters of uncoated tablets (Thickness, hardness, friability, weight variation and content uniformity of the prepared uncoated tablets):

The results of thickness, hardness and friability of all the prepared uncoated tablets are shown in table (3-4).

1- Tablet Thickness:

The thickness of a tablet from batch to batch needs to be controlled. Thickness may vary with no change in weight because of difference in the density of granulation and the pressure applied to the tablets, as well as the speed of the tablet compression. Not only is the tablet thickness important in reproducing tablets identical in appearance but also to ensure that every batch will be usable with selected packaging components. It was found that all tablets possessed uniform thickness. The thickness of prepared prednisolone uncoated tablets was in range of (3.19 ±0.01 to 3.25 ±0.02 mm) as shown in table (3-4). This minor difference with constant tablet weight was due to uniformity in die fill, good flow properties, uniform pressure and appropriate punch movement [(179)].

2- Tablet Hardness:

Tablets require a certain amount of strength or hardness to withstand mechanical shocks of destruction during handling and transportation [(149)]. The hardness of the prepared tablet was measured using electrical hardness tester and was in range of (3.5±0.06 kg/cm^2 to 5.85±0.01 kg/cm^2) for uncoated tablets as shown in table (3-4) indicating that the tablets are of adequate strength property to resist handling and mechanical stress. Adequate tablet hardness and resistance to powdering

and friability are necessary requisites for consumer acceptance. Many researches showed that the disintegration time of tablets is directly proportional with hardness of prepared tablets, as the tablets become harder, the longer was the disintegration time and perhaps a more significant effect on drug dissolution rate has become apparent [180].

3- Tablet Friability:

In order to investigate the ability of the tablets to resist chipping and abrasion on handling during packaging and shipping [149]. All the prepared tablets had acceptable friability. The weight loss was less than 1% as shown in table (3-4) which was attributed to the presence of avicel (≈70% w/w of tablet weight). Avicel is a highly compressible material because of its plastic deformation properties and high attractive force which is contributed to higher compact strength, resultant in improved skeleton integrity of the tablets and gives them acceptable friability [181].

4- Weight Variation:

The weight variation test results of all prepared tablet formulas are confirmed to the USP requirements limits (± 7.5%). It was found to be from (98±0.02 to 100±0.02 mg) the results represented in table (3-3). None of formulas was exceeding the limits of (± 7.5%) specified by USP.

5- Content uniformity test for uncoated tablets:

According to the USP specifications for assay are that the Prednisolone contents should not be less than 90 % and not more than 110% of the labeled amount of active drug. The percentage drug content in all formulations was found in the range of 98 %-100.5 %. These results indicated that the prepared dosage form had uniform distribution and proper dose of the active ingredient [151, 182].

Table (3-4): Post compression parameter of prednisolone tablets.

Formula	Thickness (mm)	Hardness (kg/ cm^2)	Friability (%)	Weight variation (mg)
F1	3.19± 0.01	4.5± 0.02	0.46±0.04	99±0.04
F2	3.19±0.03	5.02±0.04	0.1±0.05	99.5±0.01
F3	3.19±0.02	5.8±0.01	0.2±0.03	100±0.02
F4	3.21±0.01	5.5±0.02	0.25±0.05	98.5±0.01
F5	3.19±0.01	4±0.03	0.51±0.02	98±0.02
F6	3.21±0.04	4.92±0.01	0.7±0.01	99.6±0.03
F7	3.2±0.03	3.7±0.01	0.8±0.03	100±0.01
F8	3.25±0.01	4.6±0.02	0.7±0.01	100±0.02
F9	3.25±0.02	3.5±0.06	0.6±0.02	98.8±0.04
F10	3.20±0.01	4±0.03	0.6±0.01	99.7±0.01

3.3.1.3 *In-vitro* disintegration study:

In vitro disintegration time for all prepared prednisolone uncoated tablets was found to be in the range of (43-420 seconds) as shown in figure (3-20).This short disintegration time is desirable since it facilitates the dissolution and releases of the drug from the tablet. In general disintegration of tablets achieved through overcoming the cohesive strength of tablets using different types and amount of disintegrant in tablet formulation.

The type and amount of disintegrant used in preparing prednisolone uncoated tablets was 2% croscarmellose sodium of tablets weight. Croscarmellose sodium is a cross linked polymer of carboxymethyl cellulose sodium. Cross linking convert the polymer to insoluble, hydrophilic, and highly absorbent material that shows excellent swelling property. This swelling property of crosslinked croscarmellose with its unique fibrous nature offer exceptional water wicking capabilities thus make this disintegrant the most widely used in the formation of fast dissolving tablets. Croscarmellose sodium provides superior drug dissolution and disintegration characteristics, thus improving bioavailability of formulations. Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for tablets, capsules and granules. In tablet formulations, croscarmellose sodium may be used in both direct compression and wet granulation processes. Concentrations up to 5% w/w of croscarmellose sodium may be used as a tablet disintegrant although normally 2% w/w is used in tablets prepared by direct compression and 3% w/w in tablets prepared by a wet granulation process [181, 183].

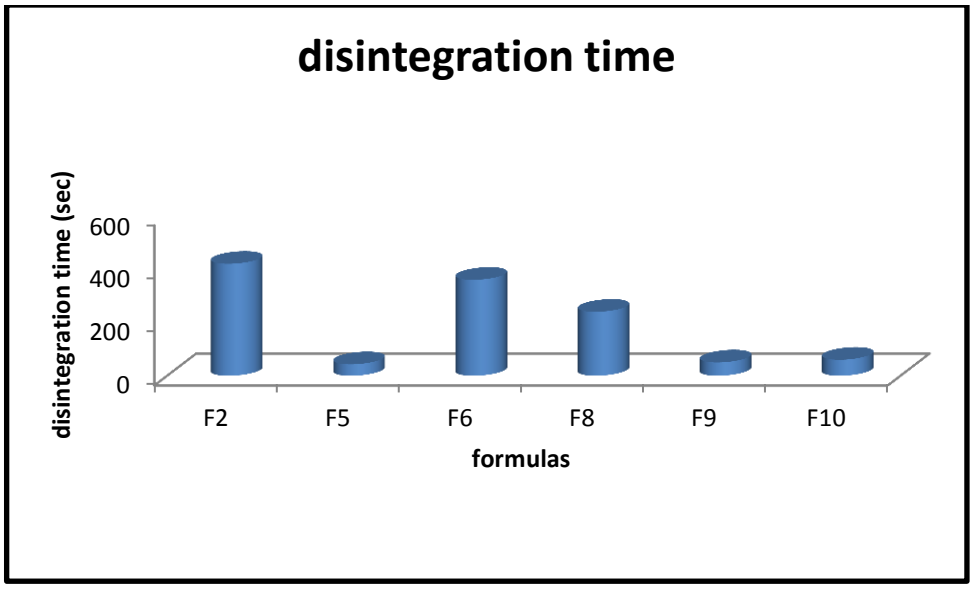


Figure (3-19): Disintegration time of solid dispersion tablets.

3.3.1.4 *In-vitro* dissolution study:

a- Effect of type of superdisintegrant addition on uncoated tablet:

Solid dispersions (F2, F3 and F4) were selected to investigate the effect of type of superdisintegrant as croscarmellose sodium, crospovidone and tablet prepared without superdisintegrant addition respectively on the drug release from uncoated tablet shown in figure (3-21). There was significant difference ($p<0.05$) between these formula which indicate that among these formulas the F2 give the best result of 100% release since the rapid increase in dissolution of prednisolone with the use of croscarmellose sodium may be attributed to rapid swelling and disintegration of tablet into apparently primary small particles while crospovidone exhibits high capillary activity and pronounced hydration with a little tendency to gel formation and disintegrates the tablets rapidly but into larger masses of aggregated particles [184]. Thus, the differences in the size distribution generated and differences in surface area exposed to the dissolution medium with different superdisintegrants rather than speed of

disintegration of tablets may be attributed to the differences in the 100% of release values with the same amount of superdisintegrants in the tablets. Thus, although the disintegration times were lower in crospovidone containing tablets, comparatively higher time to reach 100% release values were observed due to larger masses of aggregates [184, 185].

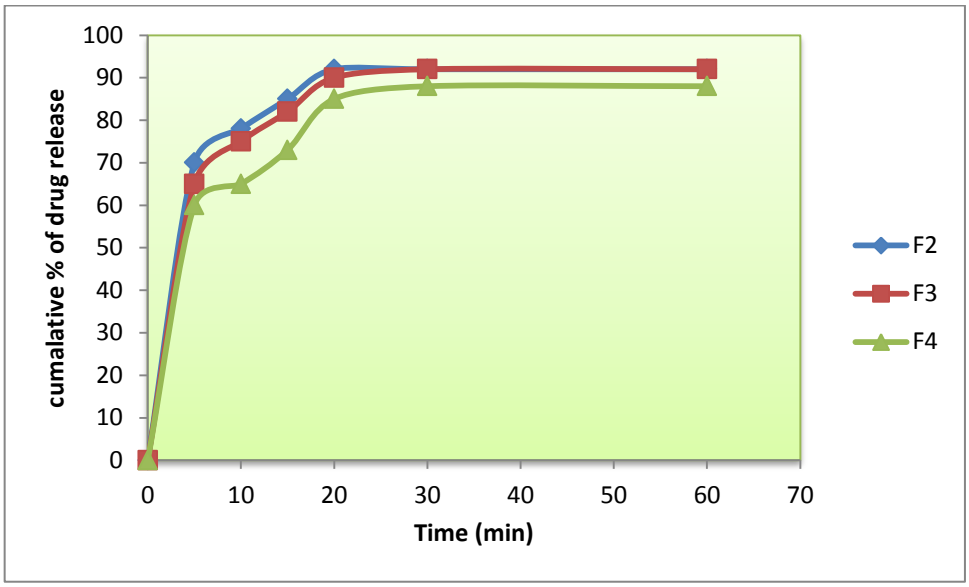


Figure (3-20): Effect of different superdisintegrant addition on uncoated tablet for F2, F3 and F4 in phosphate buffer pH7.4 at 37ºC.

b- Effect of croscarmellose sodium concentration:

The results of (F6 and F7) uncoated tablet formulas which were designed to study the effect of croscarmellose sodium concentration on drug release from uncoated tablet are shown in figure (3-22). There was a significant difference ($p<0.05$) between F6 (contain 2 % croscarmellose sodium) and F7(contain 5% croscarmellose sodium) which indicates that as the croscarmellose sodium concentration increases; the drug release increases as the disintegration time decreases since the superdisintegrant speed up the breakdown of tablet which leading to increasing surface area resulting in higher dissolution rate [184].

The increase of croscarmellose sodium concentration lead to decrease in disintegration time significantly which make it disintegrate within less than 10 sec and this is not needed in research so as a result the use of 2% concentration is preferred.

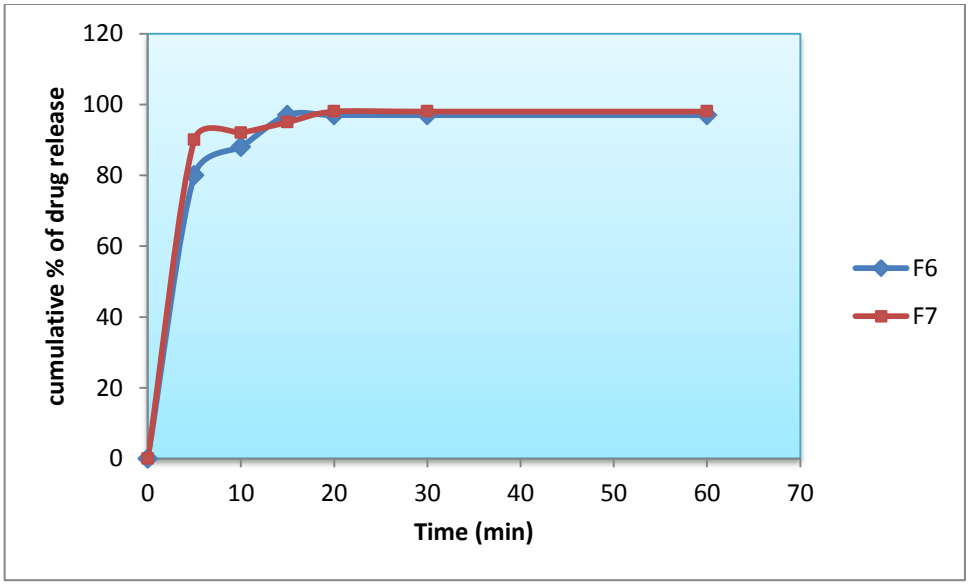


Figure (3-21): Effect of croscarmellose sodium concentration on release of F6 and F7 in phosphate buffer pH7.4 at 37°C.

c- Effect of type of polymer used in solid dispersion formulated uncoated tablets:

Figure (3-23) shows dissolution profile of prednisolone from eight different tablets solid dispersion and pure drug tablet compared to marketed uncoated tablet in phosphate buffer (pH 7.4). The percentage release of prednisolone in the first 5 minutes was 30% from tablets prepared from pure drug (F1) and that from solid dispersion formulate tablets was 70, 85, 80, 85, 70, 95 and 65 for F2, F5, F6, F8, F9, F10 and marketed tablets respectively. After 1 hour the percentage releases were (92-100), 80, 90% for prednisolone solid dispersion tablets, plain tablet and marketed tablet respectively. The release of drug from tablets

prepared from solid dispersion samples (F2, F5, F6, F8, F9and F10) was significantly higher ($p<0.05$) than that prepared from pure prednisolone.

These results are similar to those obtained from powdered prednisolone, which indicates that the enhancement in the dissolution of drug from solid dispersion samples is maintained after manufacturing these samples into tablets. However there is difference in release between different solid dispersion tablets and this may be attributed to polymer used in preparation of solid dispersion. Figure (3-23) show that among all formulations F10 prepared using Kollicoat IR showed 97.71 % drug release within 5 min while tablet prepared with D-mannitol solid dispersion showed 88% drug release after 5 min dissolution, whereas tablets prepared with PEG-4000, PEG/SLS, and PVP-k30 solid dispersion showed 70, 75 and 85% drug release respectively after the same time interval. This may be due to more hardness of the tablets as these carriers act as strong binders at higher level with in the tablets [(186)]. During compression, the carrier could plasticize, soften or melt, filling the pores within tablets and thus making them non-disintegrating. It is also possible that the soften and melted carriers coat the disintegrants and other ingredients used in tablets, and such a coating along with the reduction of porosity of tablets makes disintegration difficult [(186)]. As previously mentioned Kollicoat IR inhibits crystallinity of drugs and resulting in amorphous nature of drug in the solid dispersions. Crystallization inhibition was attributed to two effects: the interactions between the drug molecule and the hydrophilic polymer due to hydrogen bonding and the entrapment of the drug molecules in the hydrophilic polymeric matrix during solvent evaporation or a combination of both. In presence of Kollicoat IR, drug had better wettability; hence the dissolution of drug was greater in the form of solid dispersion.so this formula choose as the

optimum formula since it give fastest release compared with other formulas which also similar to that obtained for powdered prednisolone solid dispersion [137].

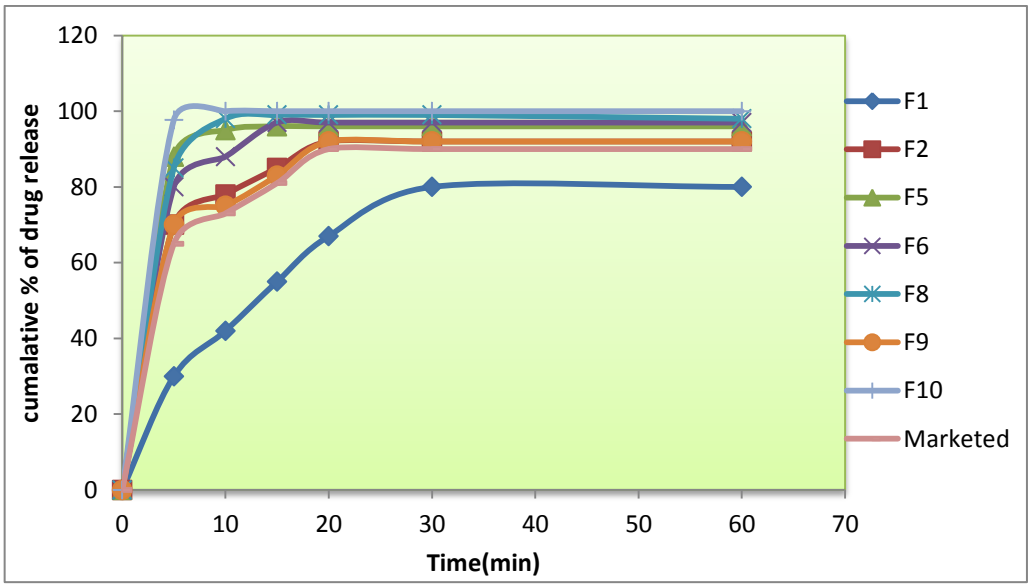


Figure (3-22): Dissolution profile of prednisolone from eight different uncoated tablets in phosphate buffer pH 7.4 at 37°C.

3.3.2 Evaluation of the prepared colon targeted tablet:

3.3.2.1 Thickness, hardness, friability, weight variation and content uniformity of the prepared coated tablet:

The developed formulation of coated tablet was studied for its physical properties like thickness, hardness, friability and weight variation as described in section(3.3.1.2) , the result was as follow; thickness was (3.66mm±0.002) , hardness was (7 Kg /cm^2±0.005), friability was 0.18% and weight variation was (116 mg±0.5). The content uniformity test was done for the selected coated tablet formula and the result was 99.95%. This result agrees with the requirements of the USP.

3.3.2.2 *In-vitro* disintegration test:

The coated tablet met pharmacopeial (BP/ USP) requirements for the enteric performance test in the HCl for 2hr, tablet disintegrate in phosphate buffer solution pH 7.4 after 20min±0.02. Also it was found that tablet coated at higher levels had longer disintegration times than that coated at lower levels in the same medium as for 16% and 19% coat level was 20 and 60min respectively [187].

3.3.2.3 *In- vitro* release study and effect of coat thickness on 100% drug release of coated tablet:

The requirement for *in vitro* release pattern selected for the colon targeting was no drug release up to the end of 5hrs to achieve this different Eudragit S100 coating level was examined and the best result was using 16% coating level using 5 times dipping in the coating solution.

The drug release was directly related to the concentration of polymer in solution and the % coating level [158]. Percent of drug release versus time plot shows that the dissolution rate was inversely proportional to the coating level applied. A significant difference was observed in the percentage of drug released for different coating level.

The selected tablet formula was used to study the effect of coat level (thickness) on lag time of colon targeted coated tablet. The 100% drug release of coated tablet which have tablet thickness 3.66mm was 5 hours and 20 min while for the same tablet formula which have tablet thickness 3.75mm was 7 hours as shown in figure (3-24). These results showed that as the thickness of the coat increased, the time to reach 100% drug release increased since the time required to complete the erosion of

the outer shell would be longer. The same results were reported with other related studies [188].

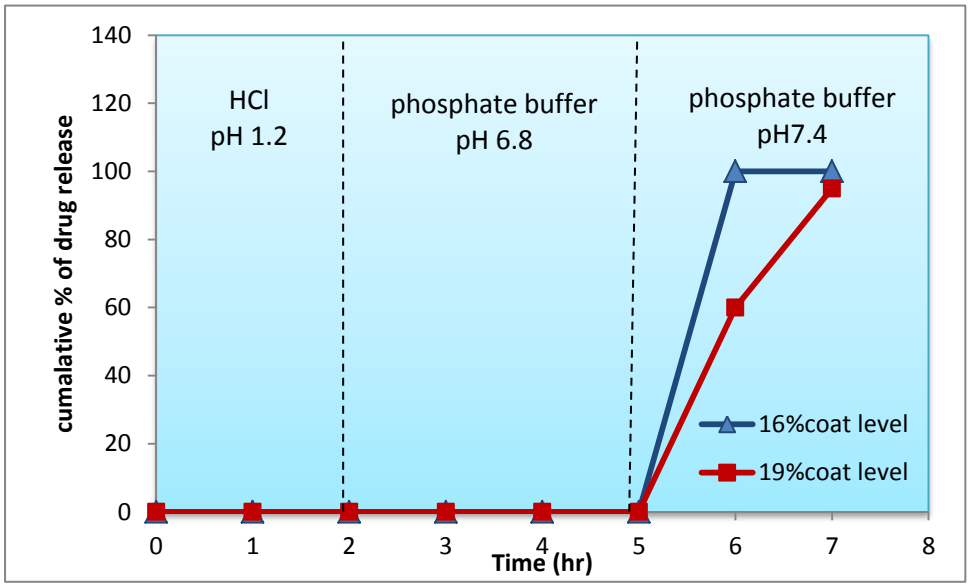


Figure (3-23): *In- vitro* release of coated tablet and effect of coat thickness on percent of drug release in different dissolution media

3.3.2.4 Drug-excipients compatibility studies:

The FTIR spectra for the pure prednisolone powder (Figure 3-5) showed characteristic absorption bands as described in section (3.1.4) previously [189]. The results showed that these bands don't change significantly in the FTIR spectra of the grinded uncoated tablet, and selected coated tablets as shown in figure (3- 25) and the small shifting in the absorption bands was listed in table (3-5). These results indicating that there is no significance evidence of chemical interaction between drug and polymer, which confirm the stability of drug.

Table (3-5): Characteristic Absorption Bands of Prednisolone

Characteristic Group	Pure Prednisolone cm^{-1}	Prednisolone core tablet cm^{-1}	Prednisolone coat tablet cm^{-1}
-OH	3454 cm^{-1}	3379.4 cm^{-1}	3354 cm^{-1}
Sp3 C-H	2982 cm^{-1}	2910 cm^{-1}	2910 cm^{-1}
-C=O	1710 cm^{-1}	1710 cm^{-1}	1730 cm^{-1}
-C=O	1654 cm^{-1}	1654 cm^{-1}	1654 cm^{-1}
Aromatic C=C	1610 cm^{-1}	1612 cm^{-1}	1610 cm^{-1}
C-H bend	1446 cm^{-1}	1437 cm^{-1}	1431 cm^{-1}
OH bend	1348 cm^{-1}	1371 cm^{-1}	1371 cm^{-1}
-C-O	1236 cm^{-1}	1240 cm^{-1}	1242 cm^{-1}
Aromatic C=C bend	893 cm^{-1}	893 cm^{-1}	895 cm^{-1}

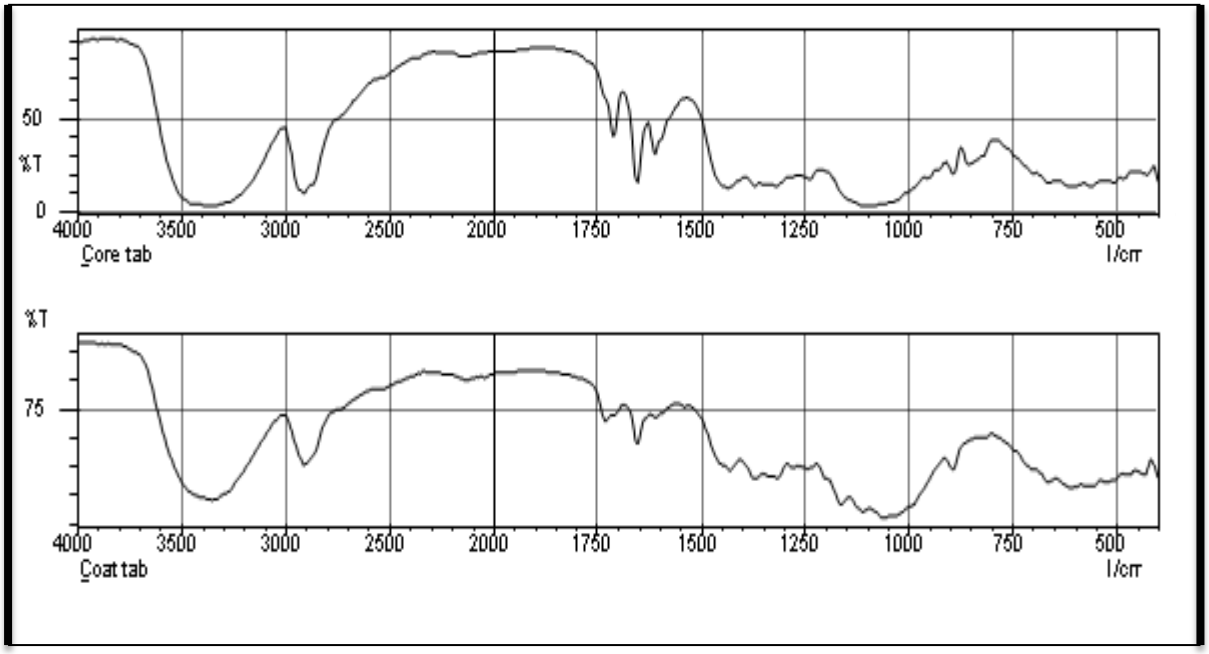


Figure (3- 24): The FTIR spectra of the grinded uncoated and coated prednisolone tablets.

3.3.2.5 Stability study: accelerated temperature effect

Accelerated stability of the selected formula (F10) after coating was studied at three different temperatures (40, 50, and 60º C) for 3 months. It was found that degradation profile follows first-order kinetics since straight line was obtained when plotting the logarithm of percent remaining versus time. Figure (3-26) shows the degradation curve of prednisolone at 40, 50 and 60°C, from which the degradation rate constant (*K*) at each temperature was determined from the slope of each line as shown in table (3-6).

Table (3-6): Degradation rate constants (K) of the selected prednisolone formula (F10) at different temperatures

Temperature (ºC)	K ($week^{-1}$)
40	2×10^{-3}
50	3.5×10^{-3}
60	6×10^{-3}

The expiration date of prednisolone was determined through constructing Arrhenius plot as shown in figure (3-27) in order to estimate the degradation rate constant (K_{25}) at 25°C . The value of K_{25} was found to be equal to 7.28×10^{-4} $week^{-1}$.

The following equation is used to calculate the expiration date of the drug follows first order kinetics [190]:

$$t_{10\%} = 0.105 / K_{25}$$

Where ($t_{10\%}$) is the time required for a drug to lose 10% of its potency and it was found to be 144 week or about 3 years since K_{25} was equal to 7.28×10^{-4} $week^{-1}$.

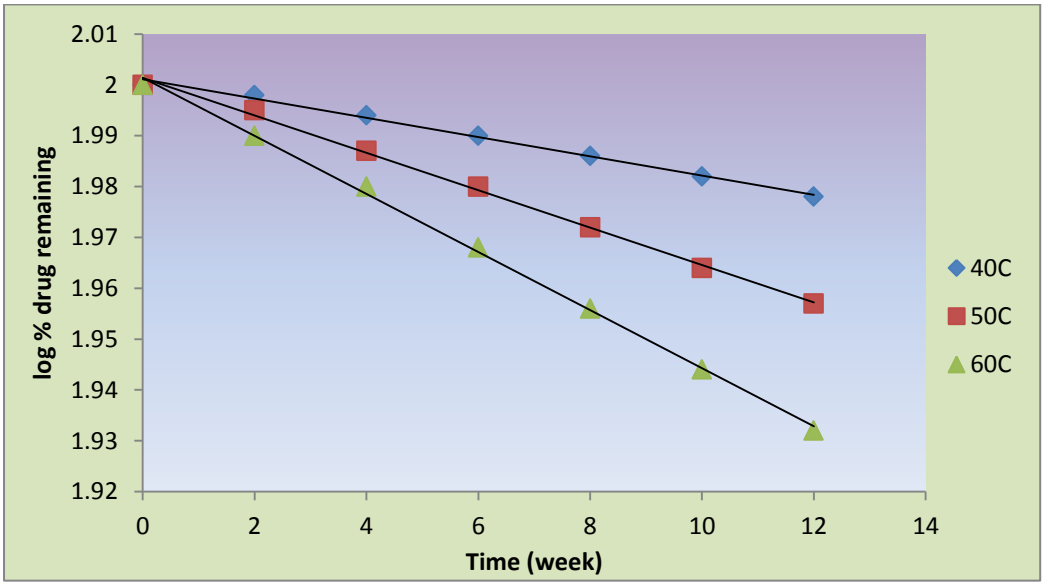


Figure (3-25): Accelerated degradation of prednisolone in the selected formula (F10) at 40, 50 and 60° C

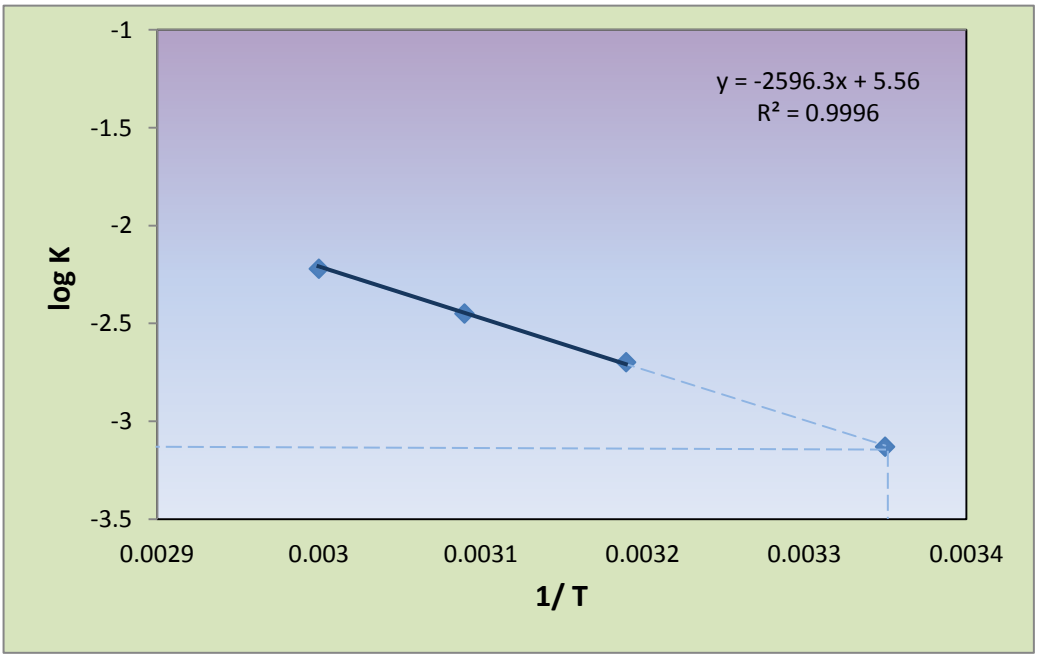


Figure (3-26): Arrhenius plot of prednisolone in the selected formula for the estimation of expiration date.

CHAPTER FOUR

CONCLUSION & RECOMMENDATION

4. Conclusion & Recommendation

4.1 Conclusion:

The present study was done to develop a colon targeted tablets containing prednisolone solid dispersion for the effective treatment of ulcerative colitis and crohn's disease.

Based on the results obtained, one can conclude the following points:

1/ Solid dispersion using solvent evaporation method is proved to be a useful technique to improve the solubility of poorly soluble drugs like prednisolone.

2/The dissolution of prednisolone from prepared solid dispersions was improved and as the polymeric content increases the dissolution rate increases consequently.

3/The highest percent of drug release and minimum time required for complete cumulative drug release was obtain with solid dispersion prepared using Kollicoat IR and PVP K30

4/Incorporation of a surfactant (SLS) into a solid dispersion of PEG4000 formula significantly improved the solubility, the dissolution rate of the drug compared to solid dispersion with PEG4000 only.

5/Among the various solid dispersion batches (Eudragit L 100, PEG 4000, PVP K30, D-Mannitol, Kollicoat IR in the ratio 1:3), best results obtained with solid dispersion prepared using (Drug: Kollicoat IR) exhibited significant enhancement in solubility and dissolution profile of the drug.

6/ SEM studies revealed the spherical nature of the drug in solid dispersion. Spherical nature indicates improvement in micrometric properties, increase surface area lead to increase solubility.

7/ DSC studies revealed the lack of melting point of drug in solid dispersion indicated that the drug was present in an amorphous form in SD18.

8/ PXRD studies revealed the decrease in the intensity of different peaks of drug in solid dispersion confirm the formation of solid dispersion by decreasing crystallinity and change to amorphous form.

9/FTIR study of the selected formula (SD18) of solid dispersion showed no chemical interactions between the drug and the carriers with partial loss of crystallinity.

10/Solid dispersion is a promising technology for formulation development of these poorly soluble drugs

11/Solid dispersion formulation was used successfully to prepare tablet for delivering the drug to colon.

12/Coating the tablets with methacrylate co-polymers (Eudragit S100) can be used as coating for targeting the drug release in colon.

13/The optimum formulation of colon targeted tablet was the one coated with 16% coating level of Eudragit S100.

14/The *in vitro* studies showed that this coated tablet successfully deliver the maximum amount of drug in intact form to the colon.

15/Inclusion of superdisintegrant (Croscarmellose) within the tablet enhance the disintegration property of tablet when reach to colon.

16/Coating of the tablet prevent the drug release in the stomach and intestine, so it can solve the problem of side effect of anti-inflammatory drug in this area & also prevents ulcerative colitis.

17/ Stability studies reveal that the product does not undergo degradation on storage and hence expected to maintain its integrity during storage with reasonable expiration date.

Recommendation:

1/The solid dispersion formulas can further be investigated for the incorporation into other dosage forms like oral solid dosage form, oral granules for reconstitution, oral dispersible powder for human or veterinary use and rectal suppositories.

2/Future *in vivo* studies are required to investigate F10 coated tablet for its performance for the *in vitro* – *in vivo* correlation.

3/Though several studies are reported on solid dispersions, intensive research in this area is still needed for making the technology applicable to industry needs.

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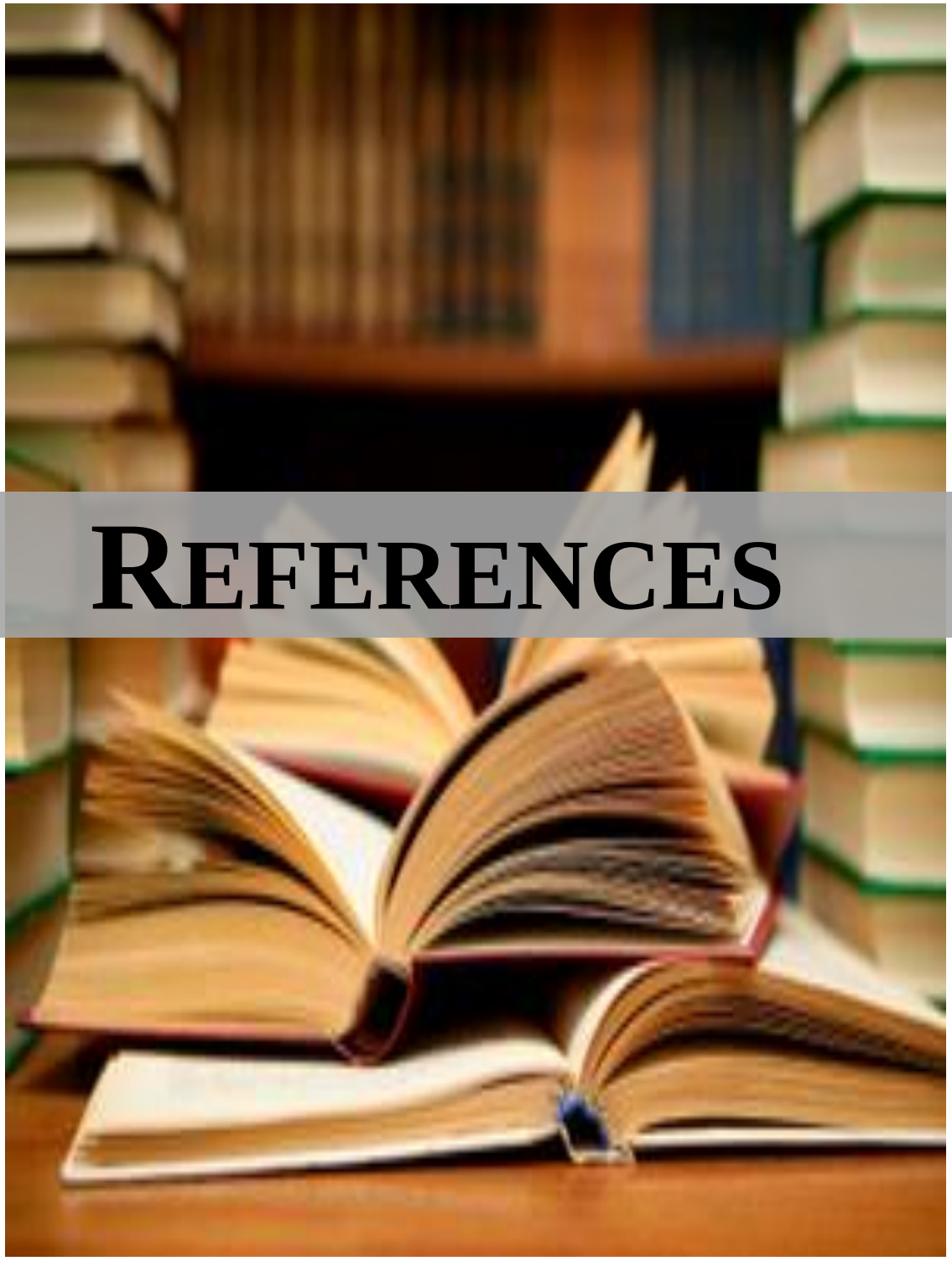

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الخلاصة

أن نظام توصيل الدواء للقولون بالتحديد اعطى اهمية للادوية التي يتم امتصاصها في منطقة القولون من خلال منع امتصاصها في الجهاز الهضمي العلوي (المعدة والامعاء الدقيقة) ولهذا فأن تحررالدواء في هذه المنطقه يضمن اقصى قدر من الفوائد العلاجية خاصة لعلاج امراض القولون الموضعية والتي يمكن ان تعالج بكفاءة اكثر من خلال توصيل الدواء للقولون بالتحديد.

البريدنيزولون هو دواء كورتيكوستيرويدي مما يجعله مفيد لعلاج مجموعة واسعه من الالتهابات ونقص المناعه مثل داء كرون ، التهاب القولون التقرحي، التهاب المفاصل الروماتويدي...كما انه يعتبر مادة من الدرجة الثانيه وفقا لنظام تصنيف الصيدله الحيوية والتي تتصف بانها مواد قليلة الذوبان بالماء ولكنها ذات نفاذية عالية..

ان المنتشر الصلب لمادة البردنيزولون باستخدام نواقل ذائبة في الماء ممكن ان يعتبر وسيله لتحسين ذوبانيته القليله بالماء وبالتالي تؤدي الى زيادة تحرر الدواء من الصيغ الدوائية وزيادة التوافر الحيوي له كل هذا يؤدي الى الحد من الاثار السلبية للصيغ الدوائية من خلال تقليل الجرع المستخدمة...

وقد اجريت هذه الدراسة من اجل صياغة اقراص مستهدفة للقولون لمادة البردنيزولون المنتشر الصلب لضمان افضل تحرر تام للدواء في المنطقه المستهدفة (القولون) حيث حضر المنتشر الصلب لمادة البردنيزولون بأستخدام انواع مختلفة من النواقل الذائبة في الماء مثل (د- مانيتول ، بولي اثيلين جلايكول (PEG4000)، بولي فنيل بايروليدين (PVP k30) وكوليكوت اي ار(Kollicoat IR)، مواد ذات التأثير السطحي الغير ايونية مثل صوديوم لوريل سلفيت والبوليمر المعوي ايودراجيت ال 100(Eudragit L100) بتراكيب مختلفة وكلها تمت بأستخدام طريقة تبخر المذيب وقد تم دراسة متغيرات مختلفة مما قد تؤثر على ذوبانية الدواء وتحرره مثل نوع الناقل ونسبته وتأثير اضافه مواد التأثير السطحي على الكثير الناقل..

كما تم تحضير الخليط الفيزيائي مع مختلف النواقل وتمت مقارنته مع المنتشر الصلب لنفس التراكيب وبعد كل هذا تم تشخيص الدواء النقي والمنتشر الصلب المختار بأستخدام تقنيات تحليلية مختلفة وقد اوضحت النتائج بأن التحضير المختار اظهر زيادة في ذوبانية الدواء وتحرره مقارنة بالدواء النقي والخليط الفيزيائي...

و قد بينت النتائج ان Kollicoat IR هو افضل ناقل لتحضير المنتشر الصلب متبوع بPVP k30 بينما النواقل الاخرى كانت الاقل تأثيرا على زيادة ذوبانية وتحرر الدواء وكذلك لاحظنا ان عمليه ادخال مواد التأثير السطحي مثل صوديوم لوريل سلفيت على المنتشر الصلب المرقم ب9 ادى الى زيادة الذوبانية بصورة ملحوظة من(354.16 الى 585.9 مايكروغم/مل) وكذلك نسبة تحرر الدواء خلال الخمس دقائق الاولى من الوقت المطلوب لتحرر الدواء التام من (72% الى 83%)...

بصورة عامة؛ كلما زادت نسبة الناقل زادت ذوبانية البردنيزولون بشكل خطي وكذلك بالنسبة لتحرر الدواء ايضا ازداد بشكل ملحوظ ومن خلال كل ماسبق ذكره لقد تم اختيار المنتشر الصلب المرقم ب18 كأفضل صيغة دوائية وكانت نسبة الدواء الى الناقل 1:3 وقد اجريت عليه بعض الفحوصات باستخدام جهاز المسح التفاضلي الكالوري و مطيافية الاشعة تحت الحمراء وحيود الاشعة السينية للمساحيق واخيرا جهاز مسح المجهر الالكتروني . واشارت هذه الفحوصات الى ان الدواء تغير في شكله من الكريستال الى الغير متبلور وانخفاض في نسبة التبلور مما يؤكد تشكيل المنتشر الصلب كما انه لا يوجد تفاعل كيميائي بين الدواء والناقل.

لقد تم صياغة الحبوب المستهدفة للقولون باستخدام افضل صيغة من المنتشر الصلب لكل ناقل من خلال كبسها على شكل حبوب سريعة التفكك باستخدام صواغ متوافقة ومن ثم تم اختيار افضل صيغة لتغليفها بالكثير المستجيب لدرجة الحامضية ايودراجيت اس 100(Eudragit S100) وتمت دراسة تأثير كل من نوع وكمية المواد الفائقة التفكك في تحضير هذه الحبوب وكذلك مستوى التغليف بالكثير لتحديد الوقت اللازم لتحرر الدواء في المنطقة المطلوبة (القولون) وكانت افضل نتيجة باستخدام 16% من مستوى تغليف الكثير..

ان نتائج هذه الدراسة اظهرت ان الصيغة المختارة قاومت التغير بالدرجة الحامضية لما قبل منطقة القولون ومنعت تحرر الدواء فيها واظهرت تأخرا كافيا في الوقت لتوجيه الدواء للقولون هو مايقارب 5 ساعات تليها مرحلة التحرر الفوري في الوسط المطلوب ذو درجة الحامضية 7.4 ولهذا ان هذه الحبوب المقترحة يمكن اعتمادها كنظام موجه للقولون لمادة البردنيزولون مع تحسين في سرعة تحرره وبالتالي توافره الحيوي...

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وزارة التعليم العالي والبحث العلمي

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كلية الصيدلة

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رسالة مقدمة الى فرع الصيدلانيات

والى لجنة الدراسات العليا في كلية الصيدلة – الجامعة المستنصرية

كجزء من متطلبات الحصول على درجة الماجستير

في علوم الصيدلة

(الصيدلانيات)

من قبل

سرى زهير محمود

بكلوريوس صيدلة (2008)

باشراف

م .د. وداد كمال علي

1437 هـ

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