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Development And Evaluation Of Immediate Release Granules For Management Of Hypertension

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Abstract

The objective of this work was to formulate and evaluate immediate release granules of Hydrochlorothiazide with Preformulation study for the management of hypertension. A diuretic drug called hydrochlorothiazide is used to alleviate swelling brought on by fluid accumulation and hypertension. Additional applications include the management of renal tubular acidosis and diabetic insipidus, as well as the reduction of kidney stone risk in individuals with elevated urine calcium levels. A thiazide drug called hydrochlorothiazide causes a natriuresis by preventing sodium and chloride ions from being reabsorbed from the kidneys' distal convoluted tubules. Hydrochlorothiazide's weak solubility and wettability contribute to its poor dissolution. Using the solid dispersion approach, the physicochemical properties of hydrochlorothiazide were improved in this study. PEG 6000 polymer was used to formulate a solid hydrochlorothiazide dispersion at three different drug: polymer ratios: 1:1, 1:2, and 1:3. The Hydrochlorothiazide Preformulation Study comprised a study of the drug's polymer interactions, standard calibration curves, melting point, and FTIR analysis. Wet granulation was used to make the hydrochlorothiazide quick release granules using varying amounts of croscarmellose sodium, a superdisintegrant. The highest solubility was observed in the solid dispersion (1:3). Formulation A4 for instant release granules displayed a maximum of 96. In 30 minutes, release. Thus, it was decided that SD3 and A4 were the optimum formulation.

Key Words: Hydrochlorothiazide, Solid dispersion, Immediate release granules, Hypertension.

Introduction

IMMEDIATE RELEASE DOSAGE FORMS:

For systemic effects, the most effective and widely used drug administration method is oral. Oral administration offers patient compliance, simplicity of intake, discomfort avoidance, and variety. When delivering poorly soluble medications, high molecular weight proteins, and peptides, the quick release solid dosage form accelerates the rate of drug release. Since most patients need their medications to take effect quickly, they must be released right away. [1-3]

Dosage forms designated as immediate release dissolve and disintegrate quickly to release the active ingredients. By utilizing a variety of carriers and diluents, immediate release is achieved without increasing or delaying the drug's absorption and release. [4-6]

Advantages Of Immediate Release Solid Dosage Forms [7-9]

- Dosage formulations with immediate release offer cost-effectiveness and enhance patient adherence.
- The medicinal composition's solubility is enhanced by the immediate release dosage form.
- A dose form with immediate release enhances stability and bioavailability.
- The dose formulations with immediate release exhibit versatility and are painless.
- The disintegration and dissolution timing are reduced by immediate release dosage formulations.
- Immediate release dose forms have the potential to mimic the solid preparation effect of a liquid preparation. In dose form with quick release, high drug loading is possible.
- Compared to liquid dose forms, immediate release dosage forms provide precise dosing.
- The instant release dose form has the potential to be easily swallowed.
- When using an immediate release mechanism, the medicine is released all at once.

NEED FOR IMMEDIATE RELEASE DOSAGE FORM [10]

- If we anticipate that the medication will dissolve or break down quickly in the stomach.
- When we anticipate having a pleasant mouthfeel.
- When there should be no medication residue in the mouth following oral delivery.
- When preparing a liquid, the dosage form for immediate release should be suitable for disguising flavor.

- ❖ Provide a quick start to action as a result of the drug dissolving and being absorbed quickly.

OTHER EXCIPIENTS USED IN THE IMMEDIATE RELEASE DOSAGE FORMS [11-13]

Super disintegrants
Bulking materials
Emulsifying agents
Flavours and sweeteners
Lubricants

SUPER DISINTEGRANT

An excipient called a disintegrant is typically added to tablet formulations to help the tablet break up or disintegrate when it comes into touch with fluids in the gastrointestinal tract. There are two times when the disintegrating agent can be combined: 1) During the intragranular phase of granule development. 2) During the second mixing stage of the granules' compaction into tablets (extragranular).

"Super disintegrating agents" have been around for a while and have a multitude of benefits, including faster tablet disintegration, effectiveness at lower concentrations, and increased intragranular effectiveness. SUPER

DISINTEGRANTS INCLUDES -:

- ❖ Natural superdisintegrant
- ❖ Synthetic superdisintegrant

NATURAL SUPER DISINTEGRANTS

Natural super disintegrating agents come from nature and are typically utilized instead of synthetic ones because they are less expensive, non-toxic, and cause no irritation. Natural superdisintegrant includes-;
Gum karaya
Mango Peel Pectin
Dehydrated banana powder
Plantago Ovata Seed Mucilage (Isapgula)
Cassia fistula gum

SYNTHETIC SUPERDISINTEGRANTS

Sodium starch glycolate (primogel), 2-8%
Low – substituted – hydroxyl propyl cellulose, 1-5%
Polacrilin potassium
Cross – linked povidone or crospovidone (kollidone), 2-5%
Cross linked carboxy methyl cellulose sodium (Ac-Di-Sol) croscarmellose sodium, 1-3%

BULKING MATERIALS

The formulation of fast-melting tablets involves the use of bulking ingredients. The bulking materials exhibit all of the qualities of a filler, diluent, and cost-cutting agent. The breakdown in the mouth is accelerated by bulking agents. Sugar-based bulking agents, such as mannitol, lactitol, directly compressible lactose (DCL), starch hydrolystate, etc., are frequently utilized. Bulking agents make up between 10% and roughly 90% of the final composition's weight. [14]

EMULSIFYING AGENTS

For immediate release tablets, emulsifying agents are crucial because they promote quick drug release and disintegration. Emulsifying chemicals are also used to increase bioavailability and stabilize immiscible mixes. The range of emulsifying agents employed in the final composition is from 0.05% to about 15% by weight. Lecithin, propylene glycol esters, alkyl sulphates, and sucrose esters are the emulsifying agents that are used. [15]

COLOURS, FLAVOURS AND SWEETENING AGENTS

The colours are employed to enhance the tablet's attractiveness. Before granulation, the colours are combined with other substances or added to the granulating agent solution. In addition to disguising taste, flavours are added to products to improve patient satisfaction. Typically, the flavours available are restricted to chewable pills, lozenges, and effervescent tablets. Since flavours are essentially volatile oils, they are added to the granules right before the tablets are compressed.

The purpose of adding sweetening agents is to give the mixture a more palatable taste and volume. Sweetening compounds that are frequently employed include mannitol, lactose, and sucrose. These days, artificial agents like cyclamates and saccharin are not employed. Lozenges and chewable pills also contain sweetening ingredients. [16-17]

LUBRICANTS

Lubricants are used to enhance tablet appearance, granule flow characteristics, and stop materials from adhering to dies and punches. Lubricants lessen friction between individual parts during compression and between the tablets and die wall while the tablet is being ejected. Stearic acid and its many salts and derivatives are the most commonly used lubricants. The second most popular lubricant for tablets is talc. The salts that are used most frequently are magnesium and calcium stearate. [18-19]

DISEASE PROFILE

A highly prevalent condition, especially after middle age, is hypertension. While it is not a disease in and of itself, it is a significant contributor to the risk of cardiovascular death. Cerebral and renal problems are also more likely to occur in hypertension patients. The quality of life during hypertension treatment is a critical health concern since many patients would stop taking their medication because of adverse effects. Therefore, therapy compliance issues will result in worse outcomes. The majority of instances of hypertension are essential, or primary, hypertension. The primary cause of hypertension remains unknown. Elevated blood pressure in the arteries is a persistent medical disease known as high blood pressure. [20]

Reasons for the selection of drugs [21-22]

- **Hydrochlorothiazide is the right drug candidate because:**

Used to treat hypertension, or high blood pressure, either by itself or in conjunction with other medications.
Used to treat swelling or edema brought on by a number of illnesses, such as heart, kidney, and liver disease. It is also used to treat edema brought on by the use of certain drugs, such as corticosteroids and estrogen.
Used to avoid kidney stones in people with excessive blood calcium levels and to treat patients with diabetes insipidus.
The plasma half-life of hydrochlorothiazide is 5.6-14.8h.
Bioavailability is 60-65%
It is a prescription drug.
Choice of drug for the prescribers.

Materials and methods:

Hydrochlorothiazide was obtained as a gift sample from Ind-Swift Laboratories Ltd. All other material like PEG 6000, croscarmellose sodium (super-disintegrant), microcrystalline cellulose, lactose, magnesium stearate, talc were also of analytical grade.

Preformulation Studies

Prior to developing the final dosage forms, a Preformulation study is conducted. The Preformulation research investigates the chemical and physical characteristics of the medicine and its excipients. Obtaining information that is helpful for the creation of stable, efficient, and bioavailable dosage forms is the primary goal of Preformulation studies. [23] Various Preformulation studies were preformed like-:

PHYSICAL APPEARANCE: Physical appearance of Hydrochlorothiazide was examined by its various organoleptic properties like colour, state, odour and taste. [24]

MELTING POINT DETERMINATION: The capillary fusion method was used to determine the hydrochlorothiazide's melting point. A capillary with one end sealed was filled with a little amount of medication, and it was maintained inverted—that is, with the sealed end facing down into the melting point device. With the help of the supplied thermometer, the temperature at which the solid medication becomes liquid was recorded. [25]

ABSORPTION MAXIMA (λmax) OF DRUG: UV absorption maxima of the drug was determined by scanning 20µg/ml solution with methanol, 0.1N HCI and phosphate buffer pH 6.8 between 200-400nm. [26]

FOURIER TRANSFORM INFRARED ANALYSIS (FTIR STUDY): The sample's infrared spectra was examined in order to identify the compounds qualitatively. Hydrochlorothiazide's infrared spectra were recorded

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using an (ALPHA-E) Fourier transformed infrared spectrophotometer. The sample was scanned at wavelength 4000cm-1 – 400 cm-1. [27]

PREPARATION OF SOLID DISPERSION BY USING FUSION (MELTING) METHOD:

PEG 6000 was melted on a water bath at 70^{0}C, then mixed with the drug and triturated till cold. The prepared solid dispersions were passed through sieve no. 80 and stored in desiccator until used. [28]

Table No. 1: Formulation of solid dispersions

Formulation codes	Drug (Hydrochlorothiazide)	Polymer (PEG 6000)	Ratio (D/P)
SD1	500 mg	500 mg	1:1
SD2	500 mg	1000mg	1:2
SD3	500mg	1500mg	1:3

Solubility studies of Hydrochlorothiazide solid dispersion:

Solubility studies for the solid dispersion of hydrochlorothiazide were carried out in distilled water. Using a magnetic stirrer, a solid dispersion containing 10 mg of hydrochlorothiazide was stirred with 10 ml of distilled water for a duration of 24 hours at room temperature. The solutions were then filtered using Whatman filter paper. The filtered solution was suitably diluted using distilled water. Subsequently, the diluted suspension left behind was filtered using Whatman filter paper. Lastly, the material was examined at 273.5 nm using a UV spectrophotometer (SHIMADZU). [29]

Dissolution studies of solid dispersion:

The solid dispersion was dissolved in vitro using a USP Type II (Paddle type) dissolving apparatus. The 900 ^{0}C of pH 6.8 phosphate buffer solution used as the dissolving medium was maintained at 37±0.50C. The medium was swirled at 75 rpm. Every five minutes for forty minutes, 10 milliliter samples were taken and fresh dissolving medium was added. The samples were analyzed with a UV spectrophotometer after being filtered at 273.5 nm, and their results were compared with a blank. After the drug release studies were finished, the percentage of drug release was calculated. [30]

Preparation of immediate release granules:

The granules were made by the wet granulation method. Lactose monohydrate, croscarmellose sodium (CCS), microcrystalline cellulose (MCC), and solid dispersion (1:3) were carefully weighed and thoroughly mixed for 15 minutes in accordance with the geometric dilution method. Polyvinyl pyrollidone (PVP) was dissolved in isopropyl alcohol and mixed with a powder blend to form a cohesive material. Following the coherent material's passage through filter number 22, it was dried at 500 ^{0}C for 20 minutes. [31]

Table No. 2: Composition of Immediate Release Granules

Ingredients (mg)	A1	A2	A3	A4
Solid dispersion equivalent to 10 mg of the drug	40	40	40	40
Croscarmellose sodium (CCS)	2	3	4	5
Microcrystalline cellulose (MCC)	63	62	61	60
Lactose monohydrate	35	35	35	35
Magnesium stearate	5	5	5	5
Talc	5	5	5	5

EVALUATION OF BLENDS [32-34]

Bulk density: Bulk density was determined by pouring weighed quantity of blend into graduated cylinder and measuring the height. Bulk density is the ratio of mass of tablet blend to bulk volume. The bulk density was calculated by using the formula.

Bulk density = $\frac{m}{Vb}$ …….eq (1)

Here, m= weight of powder (gm)

Vb= Bulk volume (cm^3)

Tapped density: Accurately weighed amount of blend poured in graduated cylinder and height was measured. Then cylinder was allowed to 100 tap under its own weight onto a hard surface. The tapping was continued until no further change in height was noted. Here Vt was the tapped volume.

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Tapped density $= \frac{m}{Vt}$ **……eq (2)**

Carr's index (compressibility index): Compressibility is the ability of powder to decrease in volume under pressure using bulk density and tapped density the percentage compressibility of powder were determined, which is given as compressibility index. It is indirectly related to the relative flow rate. Compressibility index was determined by the given formula.

Carr's index $= \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$**…….eq (3)**

Table No. 3: Compressibility index of powder flow properties

Carr's index (%)	Type of flow
5-12	Excellent
12-18	Good
18-21	Fair
23-35	Poor
33-38	Very poor
>40	Extremely poor

Hausner's ratio: Hausner's ratio indicates the flow properties of powder and measured by the ratio of tapped density to bulk density. Hausner's ratio was determined by the given formula;

Hausner's ratio $= \frac{\text{Tapped density}}{\text{Bulk density}}$**……..eq (4)**

Table No. 4: Hausner's ratio of powder flow properties

Hausner's ratio	Type of flow
1-1.1	Excellent
1.12-1.18	Good
1.19-1.25	Fair
1.35-1.45	Poor
1.46-1.59	Very poor

Angle of repose (θ): The funnel method was used to calculate the blend's angle of repose. The precisely weighed mixture was poured into the funnel. The funnel's height was modified so that the tip of the funnel barely brushed the blend's apex. The mixture was let to freely pass through the funnel onto the surface. [35] The diameter of the powder cone was measured and angle of repose was calculated using the following formula;

Angle of repose (tan θ) $= \frac{h}{r}$ **……eq (5)**

Here, h was the height and r was the radius of powder cone.

Evaluation Of Immediate Release Granules

Percentage yield:

The prepared granules were collected and weighed. The yield was calculated by dividing the measured weight by the total weight of components. The percentage yield of granules was calculated as follows;

% yield $= \frac{\text{Weight of granules}}{\text{Total weight of all components}} \times 100$**……eq (6)**

Drug content:

Accurately weighted granules were dissolved in a small quantity of methanol and then volume was made up to 100 ml with methanol. The solution was filtered through whatman filter paper and the absorbance was measured at 208nm. [36]

***In- vitro* dissolution study for immediate release granules**

Under sink conditions, the USP Type II (Paddle type) dissolving apparatus was used to perform the in vitro dissolution. The dissolving medium, 900 ml of phosphate buffer pH 6.8 solution, was kept at 37±0.50C. At 75 rpm, the medium was swirled. For thirty minutes, 10 milliliters of sample were removed every five minutes and replaced with new dissolving media. Following filtering at 273.5 nm, the samples were examined using a UV spectrophotometer in comparison to a blank. The studies on drug release were conducted, and the percentage of drug release was determined.

Drug release kinetics:

To adequately represent the observed drug release patterns, a mathematical model must be found. The dissolution profile is described by many mathematical functions that form the foundation of model-dependent approaches. Following the selection of an appropriate function, the dissolution profiles are assessed using the obtained model parameters. Model-dependent methods comprised zero, first-order, and Higuchi models. [37]

Zero order model:
Drug dissolution from dosage forms that do not disaggregate and release the drug slowly can be represented by the equation:
$Q_t = Q_o + K_o t$ …….. eq (7)
Where Q_t is the amount of drug dissolved in time t. Q_o is the initial amount of drug in the solution (most times, $Q_o = 0$) and K_o is the zero order release constant expressed in units of concentration time. Data from in-vitro drug release studies were plotted as cumulative amount of drug released versus time to study the release kinetics.

First order model:
The model has also been applied to the description of drug absorption and excretion, albeit theoretical conceptualization of this process is challenging. The release of the drug which followed first order kinetics can be expressed by the equation:
$-dc/dt = -Kc$ ……..eq (8)
Where K is first order rate constant expressed in units of $time^{-1}$.

Equation can be expressed as:
$\log C = \log C_o - Kt/2.303$……eq(9)
Where C_o is the initial concentration of drug. K is the first order rate constant and t is the time.

Higuchi Model:
In order to investigate the release of drugs that are incorporated in semi-solid or solid matrices but are water soluble or low soluble, Higuchi created a number of theoretical models. To study the dissolution from a planar system having a homogenous matrix, the relation obtained was the following.
$ft = Q = A\,[D(2C-C_s)\,C_s t]^{1/2} t$ …….. eq (10)
Where Q is amount of drug released in the time t per unit area A, C is initial drug concentration, Cs is drug solubility in matrix media and D is diffusion coefficient. The aforementioned equation is predicated on the idea that the systemic drug concentration at initialization is substantially greater than the drug's solubility. This premise is crucial because it serves as the foundation for the applied pseudo-steady state approach's rationale. Simplified Higuchi model includes
$F_t = K_H t^{1/2}$ ……..eq (11)
Where, K_H = higuchi dissolution constant.

Results And Discussion

PREFORMULATION STUDIES

PHYSICAL APPEARANCE

The drug possesses similar colour, odour, state and taste as given in official's pharmacopoeia.

Table No. 5: Organoleptic characters of Hydrochlorothiazide

Physical parameters	Observations
Colour	White
Odour	Odourless
State	Crystalline powder
Taste	Bitter

MELTING POINT DETERMINATION

The melting point of procured sample was found to be 266-268^{0}C that was in concordant with the literature value. This verified the purity and authenticity of the procured sample.

Table No. 6: Melting point of Hydrochlorothiazide

Method used	Drug	Literature value	Experimental value
Capillary fusion method	Hydrochlorothiazide	266-268^{0}C	268^{0}C

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PARTITION COEFFICIENT

The partition coefficient of Hydrochlorothiazide was found in close agreement with the literature value.

Table No 7: Partition coefficient of Hydrochlorothiazide

Method	Experimental Value	Literature value
n-octanol: distilled water	0.08	0.07 ±0.04

Data are expressed as mean ± S.D (n=3)

SOLUBILITY STUDIES

Table No. 8: Qualitative solubility data of Hydrochlorothiazide in different solvents

Solvents	Solubility
Distilled water	Slightly soluble
Methanol	Springly soluble
Ethanol	Springly soluble
Alkali Hydroxide	Soluble

Table No. 9: Quantitative solubility data of Hydrochlorothiazide

Media	Solubility (mg/ml)
Distilled water	0.039±0.05
Methanol	34.65±0.08

Data are expressed as mean ± S.D (n=3)

UV spectrum of Hydrochlorothiazide

When exposed to light in the visible or ultraviolet regions of the spectrum, molecules in solution absorb light of a specific wavelength depending on the type of electronic transition associated with the absorption. This information is typically obtained using a UV-visible spectrophotometer. The absorbance versus wavelength plot of the UV spectrum is typically used to represent it.

The "max of drug" was determined using a double beam UV-visible spectrophotometer (Shimadzu, UV-1800, Japan). A 7µg/ml methanol solution was scanned between 200 and 400 nm.

Estimation of Hydrochlorothiazide by UV-visible spectrophotometer

Preparation of stock solution

In 0.01 N NaOH, a standard stock solution of hydrochlorothiazide (100µg) was created. 0.01 N NaOH was used to dilute this solution, yielding dried concentrations ranging from 1 to 11 µg/ml. Using a UV-visible spectrophotometer, the absorbance of these solutions was measured at 273 nm with 0.01 N NaOH serving as a blank, and a standard curve was drawn versus concentration. The intercept, slope, straight line equation, and correlation coefficient were calculated using the calibration curve.

Preparation of calibration curve of Hydrochlorothiazide in 0.01N NaOH

Table No. 10(a): Calibration curve of Hydrochlorothiazide in 0.01N NaOH

Sr.no.	Concentration µg/ml	Absorbance
1	1	0.223±0.02
2	3	0.369±0.002
3	5	0.534±0.002
4	7	0.671±0.003
5	9	0.828±0.004
6	11	0.961±0.003

Table No. 10(b): Calibration curve of Hydrochlorothiazide in 0.01N NaOH

concentration µg/ml	Absorbance	Absorbance	Absorbance	Mean	SD
1	0.21	0.22	0.24	0.223	0.02
3	0.369	0.367	0.371	0.369	0.002

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5	0.536	0.534	0.532	0.534	0.002
7	0.671	0.668	0.673	0.671	0.003
9	0.828	0.825	0.832	0.828	0.004
11	0.961	0.958	0.963	0.961	0.003

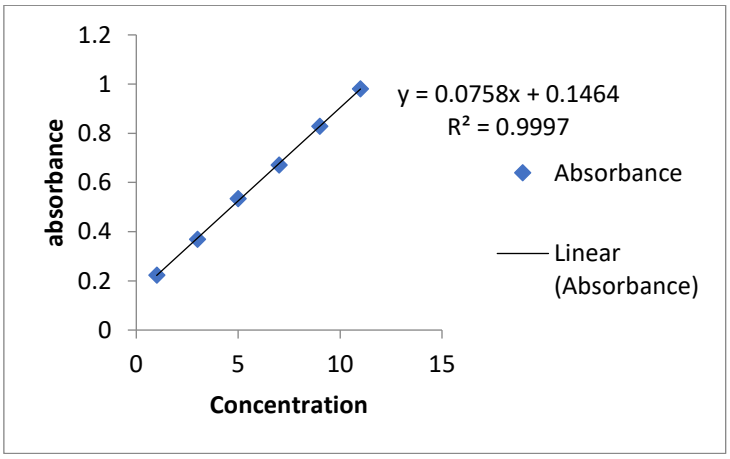

Fig 1: Standard Plot of Hydrochlorothiazide

FOURIER TRANSFORM INFRARED ANALYSIS (FTIR):. This further verified the authenticity of the drug. The FTIR spectra of Hydrochlorothiazide were shown in fig 5.8.

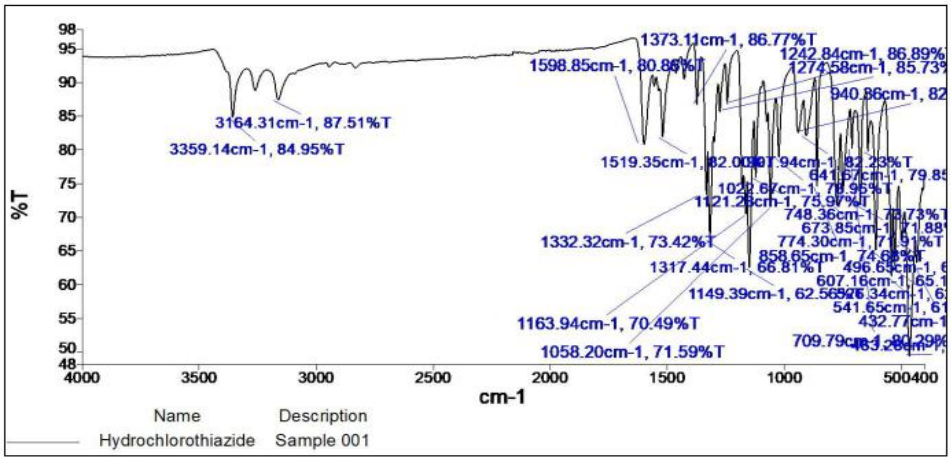

Fig 2: FTIR spectra of Hydrochlorothiazide

Solid Dispersion By Using Melting Method

Solubility profile of pure drug and solid dispersions is shown in Table 5.16. It was found that the solubility of drug increased with the increase in concentration of the polymer SD3 (1:3) showed maximum solubility. This may be due to the wetting property and solubilisation effect of the polymer. Solid dispersion SD3 (1:3) also showed maximum drug release (96.77%) corresponding to 40 minutes. Hence this ratio was selected for the preparation of immediate release granules.

SOLUBILITY DATA OF SOLID DISPERSION

Table No. 11: SOLUBILITY DATA OF SOLID DISPERSION

Formulation code	Solubility (mg/ml)
Pure drug	**0.036±0.0131**

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SD1	**0.113±0.0108**
SD2	**0.255±0.0132**
SD3	**0.435±0.0152**

Data are expressed as mean ± S.D (n=3)

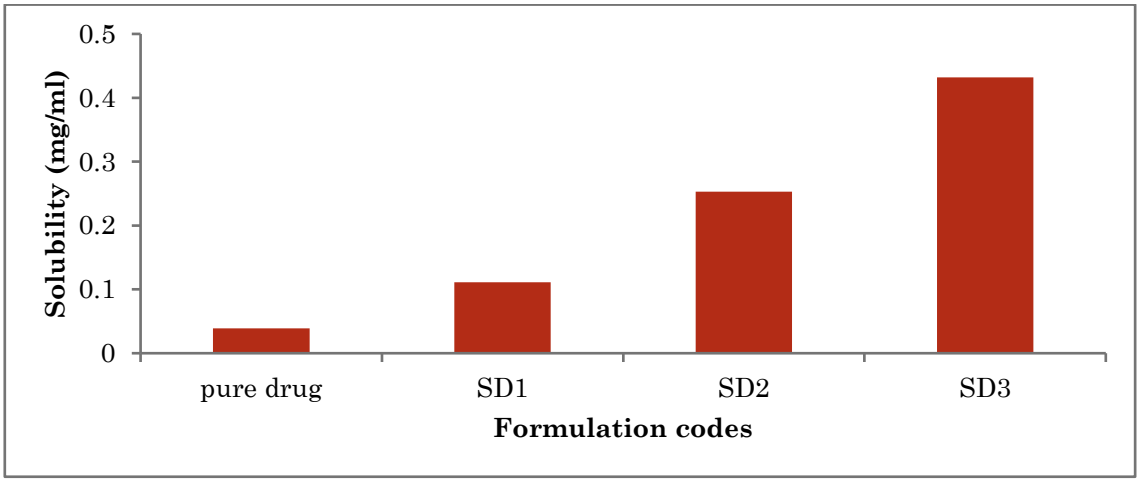

Fig 3: Solubility values of solid dispersion of different batches

Dissolution Study Of Solid Dispersion

Table No. 12: Percentage drug release from solid dispersion

Time (minutes)	Pure drug	SD1 (1:1)	SD2 (1:2)	SD3 (1:3)
5	**8.56 ± 0.18**	**15.75± 0.46**	**22.26± 0.67**	**26.68± 0.35**
10	**13.58± 0.39**	**24.06± 0.67**	**34.23± 0.75**	**37.44± 0.24**
15	**17.78± 0.49**	**32.07± 0.33**	**41.28± 0.54**	**49.18± 0.57**
20	**22.55± 0.54**	**41.26± 0.76**	**53.38± 0.62**	**61.72± 0.54**
25	**29.49± 0.37**	**48.56± 0.38**	**61.25± 0.37**	**69.93± 0.33**
30	**34.29± 0.49**	**56.57± 0.65**	**70.83± 0.29**	**77.43± 0.48**
35	**38.47± 0.57**	**62.55± 0.55**	**77.47± 0.46**	**86.47± 0.26**
40	**41.36± 0.27**	**68.83± 0.45**	**84.27± 0.44**	**96.75± 0.59**

Data are expressed as mean ± S.D (n=3)

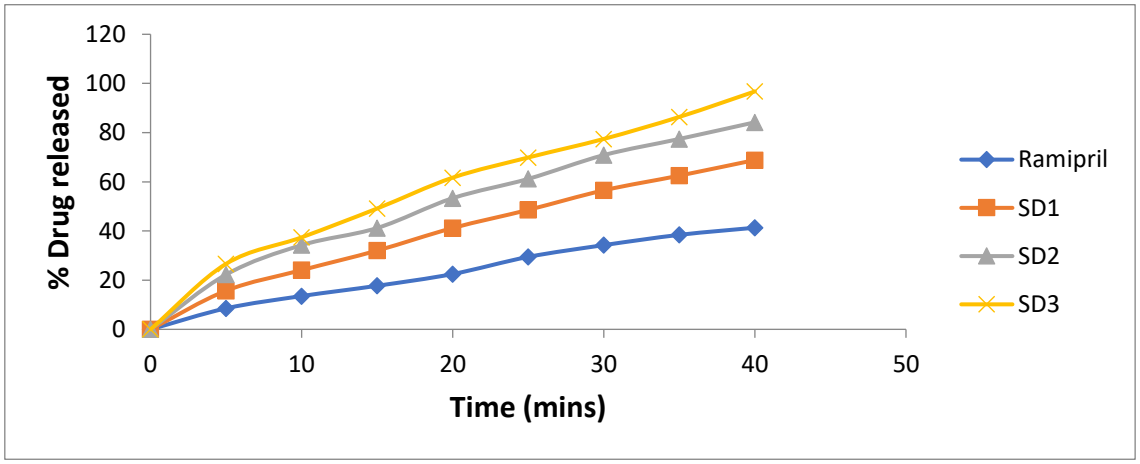

Fig. 4: Percentage drug release from solid dispersion

EVALUATION OF IMMEDIATE RELEASE GRANULES
EVALUATION OF POWDERS

Table No. 13: EVALUATION PARAMETERS OF POWDER BLEND

Formulation codes	Angle of repose (θ)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's index (%)	Hausner's ratio
A1	30.23±0.025	0.412±0.22	0.554±0.192	25.63±0.026	1.344±0.0243
A2	27.48±0.030	0.443±0.17	0.583±0.025	24.01±.030	1.316±.0233
A3	32.12±0.030	0.429±0.29	0.525±0.022	18.28±0.036	1.223±0.0152
A4	31.62±0.020	0.432±0.14	0.532±0.015	18.79±0.034	1.231±0.0123

Data are expressed as mean ± S.D (n=3)

Evaluation Of Immediate Release Granules

The percentage yield and percentage drug content was determined for all the formulations. The percentage yield for all the formulation was found to be from 79.20% to 94.21% as shown in Table No. 14.

Table No. 14: PERCENTAGE YIELD

Formulation codes	% yield
A1	79.20±0.9
A2	87.80±0.8
A3	88.6±0.8
A4	94.21±0.5

Data are expressed as mean ± S.D (n=3)

The drug content for all the formulation was found to be from 76.58% to 95.86% as shown in Table 15.

Table No. 15: % DRUG CONTENT

Formulation codes	% drug content
A1	76.58±0.6
A2	86.32±0.2
A3	88.62±0.9
A4	95.86±0.4

Data are expressed as mean ± S.D (n=3)

Dissolution Study Of Immediate Release Granules

Table No. 16: % Cumulative drug released from immediate granules

Time (min)	A1	A2	A3	A4
5	27.65±0.151	32.64±0.194	39.22±0.254	47.59±0.143
10	42.18±0.253	45.77±0.136	53.78±0.135	58.65±0.207
15	46.21±0.121	55.25±0.294	66.50±0.176	69.04±0.426
20	57.72±0.163	66.82±0.183	77.55±0.294	82.73±0.370
25	66.94±0.142	73.30±0.314	84.77±0.564	91.78±0.335
30	72.68±0.211	78.25±0.111	88.67±0.295	96.92±0.264

Data are expressed as mean ± S.D (n=3)

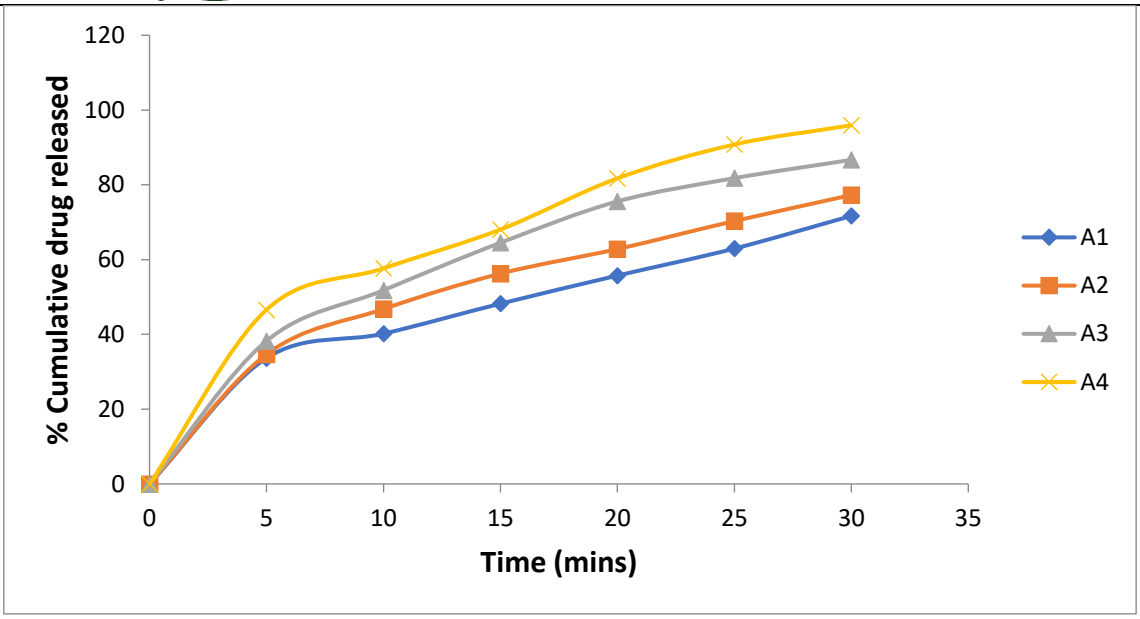

Fig 5*: In- vitro* drug release of Hydrochlorothiazide (A1-A4)

The formulation code A4 showed maximum drug release (96.92%) corresponding to 30 minutes. There was an enhancement in the drug release as the concentration of superdisintegrant increased. Hence A4 formulation was the best formulation.

Conclusion:

It is possible to draw the conclusion from this investigation that PEG 6000 improved the drug's rate of solubility when compared to pure, untreated medication. A good superdisintegrant for making granules with instant release is croscarmellose sodium. Regarding angle of repose, bulk density, tapped density, Carr's index, Hausner's ratio, drug content, and dissolving results, all of the evaluation metrics met pharmacopeal requirements. The solubility of hydrochlorothiazide was enhanced by creating a solid dispersion (by applying melting technique). PEG 6000 was used in several ratios, such as 1:1, 1:2, and 1:3, in conjunction with the medicine. Granules with immediate release were made using wet granulation. The disintegrating agent of choice was sodium cross-carmellose. Sustained release microparticles were made using a solvent evaporation method. The polymer, ethyl cellulose, was used in different proportions to the drug. The gelatin capsules underwent a precise 6-hour lag period after being treated with formalin vapour. The mass volume relationships and flow characteristics of the blend were assessed. The constructed mixed blends demonstrated adequate compressibility and appropriate flow qualities, as indicated by the results of bulk density, tapped density, hausner's ratio, compressibility index, and angle of repose. A number of characteristics, including percentage yield, drug content, and in vitro release response, were also assessed and looked at for the immediate release granules. In 30 minutes, formulation A4 produced the highest release and demonstrated the best results. As a result, this formulation helps with the treatment of myocardial infarction and mild to severe hypertension.

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